

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF DELAWARE**

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FEDERAL TRADE COMMISSION

Plaintiff,

v.

SHIRE VIROPHARMA INC.

Defendant.

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C.A. No. 1:17-cv-00131-RGA

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**APPENDIX TO OPENING BRIEF IN SUPPORT OF  
MOTION TO DISMISS BY SHIRE VIROPHARMA INC.**

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*Counsel for Shire ViroPharma Inc.*

Dated: April 10, 2017

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# EXHIBIT 1



0531 '06 MAR 17 P2:28

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March 17, 2006

VIA HAND DELIVERY

Division of Dockets Management  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

**PETITION FOR STAY OF ACTION**

ViroPharma Incorporated respectfully submits this petition pursuant to 21 CFR 10.35 requesting the Food and Drug Administration immediately stay the effective date of the following matter:

**DECISION INVOLVED**

For the reasons described below, ViroPharma requests a stay of any Agency action that would result in the approval of an Abbreviated New Drug Application (ANDA) referencing Vancocin® (vancomycin capsules) as its reference listed drug (RLD). ViroPharma requests such stay of action in the absence of evidence that the Agency has established and applied appropriate standards for approving a generic vancomycin capsule product.

**ACTION REQUESTED**

ViroPharma will shortly submit scientific evidence to present to the FDA formally requesting that the Agency:

- (a) Require using the most rigorous scientific method that will demonstrate a rate and extent of drug release to the site of action consistent with good medicine and science;
- (b) Require a demonstration that the stability of a generic vancomycin product is at least as good as the RLD;

- (c) Require the ANDA applicant relying on Vancocin to provide evidence that its product is bioequivalent to Vancocin along the entire gastrointestinal tract
- (d) Convene a joint meeting of the Advisory Committee for Pharmaceutical Science and the Advisory Committee for Anti-infective Drug Products, with industry participation, to examine the relevant data and information relating to vancomycin delivery to the GI tract for the purpose of developing appropriate and consistent standards for the approval of new products by generic applicants;
- (e) Validate with both the FDA Medical Policy Coordinating Committee and the FDA Biopharmaceutics Coordinating Committee the scientific and medical appropriateness of the approval standards for a generic locally acting vancomycin capsule product.
- (f) Provide an opportunity for public review and comment on the appropriate approval standards for a generic locally acting vancomycin capsule product.

### STATEMENT OF GROUNDS

The agency should grant ViroPharma's Petition for Stay of Action because it satisfies the criteria set forth in 21 CFR 10.35(e).

The public interest would be served by the Agency establishing standards for the approval of a locally acting vancomycin capsule product, a product that is used for treating serious, life threatening infections. For safety and reliability purposes, FDA should not apply unsubstantiated and potentially inadequate bioequivalence standards for such a serious drug.

Approving a generic vancomycin capsule product relying on Vancocin as the RLD based on inadequate demonstration of bioequivalence, has the potential of causing ViroPharma irreparable harm. If the composition of a generic vancomycin capsule raises safety issues, or its local release cannot be effectively measured to show therapeutic equivalence the reputation and goodwill that ViroPharma has established in this field may be destroyed.

ViroPharma respectfully requests that the Agency stay approval of a generic vancomycin capsule in good faith and for non-frivolous reasons. ViroPharma believes the FDA must define a bioequivalence standard in order to ensure the approval of safe and efficacious new products. Standing alone, matching *in vitro* release cannot demonstrate bioequivalence for non-systemically absorbed products like Vancocin. For a drug used for life threatening infections, this is particularly inappropriate.

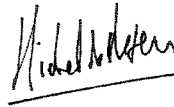
Sound public policy supports a stay in this case. In addition to medical and scientific arguments for establishing bioequivalence standards, the public has an interest in requiring an agency such as FDA to act lawfully, to fulfill obligations under its governing statutes and implementing regulations and to treat regulated parties fairly and equally.

Vancocin, the RLD that a generic vancomycin capsule would rely on in its ANDA, is safe and efficacious for patients. The approval process for an ANDA, however, must be in a manner in which the public can place their confidence. Thus, any delay resulting from a stay would not be outweighed by other interests. Although there is a public interest in lawful generic competition, there is a greater interest in ensuring that generic drugs meet the fundamental statutory and regulatory requirements for approval, i.e., are truly the same as the reference listed drugs to which they claim to be equivalent.

### CONCLUSION

For the foregoing reasons this Petition for Stay of Action should be granted.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Michel de Rosen", is written over a horizontal line.

Michel de Rosen  
Chief Executive Officer  
ViroPharma Incorporated

# EXHIBIT 2



January 11, 2008

0059 8 JAN 14 A9:04

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

397 Eagleview Boulevard  
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<sup>0124</sup>  
**RE: Docket No. 2006P-1024**

Dear FDA:

On March 17, 2006 (as amended March 30, 2006), ViroPharma Incorporated filed a petition seeking to stay approval of any new drug applications filed under Section 505(j) or Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act ("FDCA") (collectively, "ANDAs") that reference Vancocin® (vancomycin hydrochloride capsules) and rely on a new *in vitro* bioequivalence test emanating from FDA's Office of Generic Drugs ("OGD") (FDA Docket Number 2006P-0124, the "Vancocin docket"). ViroPharma has filed to this docket a number of supplements and amendments to its petition since that date.

On August 29, 2007, ViroPharma filed to FDA Docket Number 2007D-0168 comments on the Draft Guidance for Industry on Bioequivalence Recommendations for Specific Products (the "Draft BE Guidance").

On January 7, 2007, ViroPharma, certain of its advisors, and subject matter experts met with representatives of FDA's Office of Pharmaceutical Sciences (OPS), Office of Generic Drugs (OGD) and FDA legal counsel. During this meeting, ViroPharma provided a variety of information to FDA, including a discussion of procedural deficiencies noted by ViroPharma related to OGD's bioequivalence recommendation for Vancocin. This discussion referenced the comments made by ViroPharma on the Draft BE Guidance.

In the meeting, FDA confirmed that transparency and process were important to its mission, and FDA counsel requested that ViroPharma file the above-referenced comments on the Draft BE Guidance to the Vancocin docket. Accordingly, those comments are attached hereto for filing to this Docket Number 2006P-0124.

Respectfully submitted,

A handwritten signature in blue ink, appearing to read "T. Doyle" with a stylized flourish at the end.

Thomas F. Doyle  
Vice President, Strategic Initiatives  
ViroPharma Incorporated

# EXHIBIT 3



## DEPARTMENT OF HEALTH &amp; HUMAN SERVICES

Docket No. FDA-2006-P-0007

Food and Drug Administration  
Rockville MD 20857

APR 9 2012

- Thomas F. Doyle  
ViroPharma, Inc.  
730 Stockton Drive  
Exton, PA 19341

Re: Docket No. FDA-2006-P-0007<sup>1</sup>

Dear Mr. Doyle:

This letter responds to your citizen petition for a stay of action dated March 17, 2006, and amended March 30, 2006 (petition), concerning how abbreviated new drug application (ANDA) applicants, or applicants submitting applications under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for vancomycin hydrochloride (HCl) (vancomycin) oral capsule drug products, may establish bioequivalence to Vancocin HCl Capsules (new drug application (NDA) 050606), the reference listed drug (RLD) product. In summary, you have petitioned the U.S. Food and Drug Administration (FDA or the Agency): (1) to stay approval of any ANDA or 505(b)(2) application for vancomycin capsules;<sup>2</sup> (2) to rescind the 2008 draft guidance for Vancomycin Hydrochloride (Draft Vancomycin BE Guidance)<sup>3</sup> that recommends a methodology for establishing the bioequivalence of vancomycin capsules to the innovator drug product, Vancocin, using in vitro dissolution data; and (3) to require any applicant seeking to demonstrate bioequivalence to Vancocin to use in vivo data from clinical endpoint studies. You have raised scientific, legal, and procedural challenges to FDA's bioequivalence recommendation. In addition, in a recent submission, you claim that changes to Vancocin's labeling approved on December 14, 2011, are based on new clinical safety and efficacy data to which ViroPharma holds exclusive rights, and that generic vancomycin capsule products that omit this information should not be approved for 3 years from the December approval date.

<sup>1</sup> This citizen petition was originally assigned docket number 2006P-0124/PSA1 and PSA2. The number was changed to FDA-2006-P-0007 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008.

<sup>2</sup> ViroPharma seeks a stay of approval of any application filed under section 505(j) or 505(b)(2) of the FD&C Act that references Vancocin. For simplicity's sake, this petition response addresses FDA's recommended bioequivalence methodologies for vancomycin capsules in the context of ANDAs submitted under section 505(j). We note here that the Agency's discussion of, and conclusions with respect to, demonstrating bioequivalence to Vancocin set forth in this petition response also are applicable to applications submitted under section 505(b)(2) of the FD&C Act that seek to submit bioequivalence data to bridge to the finding of safety and effectiveness for Vancocin. We note, however, that in contrast to section 505(j), section 505(b)(2) of the FD&C Act does not require an applicant to demonstrate bioequivalence.

<sup>3</sup> Draft Guidance for Vancomycin Hydrochloride (Dec. 2008).

In addition to your original submission and the amendment thereto, you have filed 20 supplements to the petition and 16 submissions to the related FDA Docket No. 2008-D-0626 that concerns the Draft Vancomycin BE Guidance.<sup>4</sup> You have presented materials to an FDA advisory committee considering vancomycin bioequivalence methodologies, you have met directly with Agency representatives to discuss your position, and numerous congressional inquiries have been submitted on your behalf.<sup>5</sup>

FDA has carefully considered the issues that you have raised, other submitters' comments to the citizen petition docket and the Draft Vancomycin BE Guidance docket that concern the issues in your petition and supplements, the relevant scientific and legal authorities, and additional relevant material, including an FDA advisory committee's unanimous endorsement of FDA's 2008 bioequivalence recommendation for vancomycin. Upon review, FDA has determined that the recommendation in the Draft Vancomycin BE Guidance is scientifically sound, that FDA has clear legal authority to recommend in vitro dissolution data to demonstrate the bioequivalence of generic vancomycin, and that the process by which the Agency developed the current recommendation involved a robust, public consideration of the issues raised in your petition, in accordance with the relevant legal authorities. Finally, the Agency has concluded that under the limitation provision in section 505(v) of the FD&C Act, Vancocin is not eligible for 3 years of exclusivity for the recently approved changes to the Vancocin label. Your petition is granted in part to the extent that you request and have been provided notice of and an opportunity to comment on FDA's recommended bioequivalence methodology for generic vancomycin capsules, and FDA has provided data underlying the scientific bases for that recommendation directly to you in response to your Freedom of Information Act (FOIA) requests. Your petition otherwise is denied, as explained in detail below.<sup>6</sup>

## I. BACKGROUND

### A. Vancocin Capsules

FDA approved a new drug application (NDA) for Vancocin Capsules in 1986 for the treatment of enterocolitis in the gastrointestinal (GI) tract caused by *Staphylococcus aureus* (including methicillin-resistant strains) (SAE) and diarrhea associated with *Clostridium difficile* (CDAD).<sup>7</sup> Vancocin is only one of two FDA-approved therapies

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<sup>4</sup> Some of your submissions were cross-filed in both the citizen petition and draft guidance dockets. For the sake of efficiency, your individual supplements to this citizen petition will be referred to in the following form: "VP [insert date] Supp." Any submissions made by others or by you to other agency dockets or matters will be identified accordingly.

<sup>5</sup> See, e.g., Letter fr. Hon. A. Specter to A. von Eschenbach, M.D. (Dec. 29, 2006) (letter inquiry into appropriate bioequivalence methodology for ViroPharma's Vancocin product).

<sup>6</sup> Concurrent with this response, FDA is approving three ANDAs for generic vancomycin capsules. A final guidance for vancomycin hydrochloride bioequivalence consistent with this citizen petition response is forthcoming.

<sup>7</sup> Vancocin HCl Capsules Package Insert (Vancocin PI), at 2, available at [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/050606s0281bl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/050606s0281bl.pdf). FDA originally approved Vancocin Capsules under then-section 507 of the FD&C Act, the statutory provision under which antibiotic

indicated for treatment of CDAD.<sup>8</sup> The active ingredient in Vancocin Capsules is vancomycin hydrochloride, a tricyclic glycopeptide antibiotic derived from *Amycolatopsis orientalis* (formerly *Nocardia orientalis*). Vancomycin acts locally in the GI tract by inhibiting cell wall biosynthesis in gram-positive bacteria, and is poorly absorbed after oral administration, meaning it does not enter the body systemically.<sup>9</sup> The labeling also lists as ingredients F-D & C Blue No. 2, gelatin, iron oxide, polyethylene glycol, titanium dioxide, and other inactive ingredients.<sup>10</sup>

#### B. Applicable Statutory and Regulatory Framework

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the FD&C Act, which established the ANDA approval process for generic drugs.<sup>11</sup> To obtain approval, an ANDA applicant is not required to provide independent evidence of the safety and effectiveness of the proposed generic drug product. Instead, the applicant relies on FDA's previous finding that the RLD is safe and effective.<sup>12</sup> The ANDA applicant must identify the listed drug on which it seeks to rely and, with limited exceptions, a drug product described in an ANDA must contain the same active ingredient, conditions of use, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the listed drug it references.<sup>13</sup>

The ANDA applicant also must demonstrate that its proposed generic drug is bioequivalent to the RLD it references.<sup>14</sup> The statute, regulations and case law give FDA

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products were approved prior to 1997. As discussed in detail below in section II.C.9.b., Congress incorporated antibiotic approval into section 505 of the FD&C Act in 1997.

<sup>8</sup> On May 27, 2011, FDA approved NDA No. 201699 submitted by Optimer Pharmaceutical Inc. for Difidid (fidaxomicin) tablets for the treatment of *Clostridium difficile*-associated diarrhea in adults.

<sup>9</sup> Vancocin PI, at 9. See also id. at 3 ("[t]his preparation for the treatment of colitis is for oral use and is not systemically absorbed"). During multiple dosing of 250 mg every 8 hours for 7 doses, fecal concentrations of vancomycin in volunteers exceeded 100 mg/kg in the majority of samples. No blood concentrations were detected and urinary recovery did not exceed 0.76%. In anephric subjects with no inflammatory bowel disease who received vancomycin oral solution 2 g for 16 days, blood concentrations of vancomycin were less than or equal to 0.66 µg/mL in 2 of 5 subjects. No measurable blood concentrations were attained in the other 3 subjects. Following doses of 2 g daily, concentrations of drug were >3100 mg/kg in the feces and <1 µg/mL in the serum of subjects with normal renal function who had *C. difficile*-associated diarrhea. Id. at 9. As noted on the label, there is a possibility of systemic absorption for patients who have taken multiple oral doses of Vancocin for active *C. difficile*-associated diarrhea, and patients with inflammatory disorders of the intestinal mucosa. Id. at 3.

<sup>10</sup> Id. at 8.

<sup>11</sup> *Drug Price Competition and Patent Term Restoration Act of 1984*, Pub. L. No. 98-417, 98 Stat. 1585.

<sup>12</sup> A reference listed drug or RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations*, generally known as "the Orange Book."

<sup>13</sup> Sections 505(j)(2)(A) and (j)(4) of the FD&C Act. See also 21 CFR 314.94(a).

<sup>14</sup> See, e.g., section 505(j)(2)(A)(iv) of the FD&C Act (requiring "information to show that the new drug is bioequivalent to the listed drug"); 21 CFR 314.94(a)(7) (requiring, as part of ANDA content and format, information to show that the drug product is bioequivalent to the reference listed drug); 21 CFR 314.127(a)(6)(i) (providing that FDA will refuse to approve an ANDA if information submitted is insufficient to show that the drug product is bioequivalent to the RLD referred to in the ANDA).

considerable flexibility in determining how this requirement is met. Section 505(j)(8)(B)(i) of the FD&C Act states that a generic drug is bioequivalent to the listed drug if:

the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses . . .<sup>15</sup>

Section 505(j)(8)(C) of the FD&C Act provides that different approaches to demonstrating bioequivalence may apply to locally acting, nonsystemically absorbed drug products:

For a drug that is not intended to be absorbed into the bloodstream, the Secretary may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect.<sup>16</sup>

Such methods include using in vivo data (data from a study on human subjects), or in vitro data (data from laboratory studies). FDA's wide discretion to determine appropriate bioequivalence standards is reflected in Congress's requirement that FDA publish in the Orange Book "whether in vitro or in vivo bioequivalence, or both such studies, are required for applications filed under [section 505(j)] which will refer to the drug published."<sup>17</sup>

FDA's regulations likewise reflect the flexibility that FDA has in choosing the appropriate methods to establish bioequivalence for particular drug products. Under the bioequivalence regulations in 21 CFR part 320, the bioequivalence requirement is defined as "a requirement imposed by the Food and Drug Administration for in vitro and/or in vivo testing of specified drug products which must be satisfied as a condition of marketing."<sup>18</sup> Section 320.24, which sets out the types of evidence that may be used to establish bioequivalence, provides that:

FDA may require *in vivo or in vitro testing, or both*, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug

<sup>15</sup> See also 21 CFR 320.1(e) and 320.23(b).

<sup>16</sup> Congress enacted this provision as part of the *Medicare Prescription Drug, Improvement, and Modernization Act of 2003* (MMA), Pub. L. 108-173, 117 Stat. 2066 (Dec. 8, 2003). Congress made clear that subsection 505(j)(8)(C) codified the Agency's long-standing authority to make bioequivalence determinations. See *id.* at section 1103(b) ("[t]he amendment made by subsection (a) does not alter the standards for approval of drugs under ... 21 U.S.C. 355(j)").

<sup>17</sup> Section 505(j)(7)(A)(i)(III) of the FD&C Act; see also *Schering Corp. v. FDA*, 51 F.3d 390, 398 (3d Cir. 1995) (noting that this provision "vests the FDA with the discretion to determine whether in vivo or in vitro bioequivalence studies, or both, will be required for the approval of generic drugs under the abbreviated approval process").

<sup>18</sup> 21 CFR 320.1(f).

products . . . . The selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Applicants shall conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in paragraph (b) of this section. The method used must be capable of measuring bioavailability or establishing bioequivalence, as appropriate, for the product being tested.<sup>19</sup>

(Emphasis added.)

Section 320.24(b) of FDA's regulations describes preferred bioequivalence methods in what, for systemically absorbed products, is the descending order of accuracy, sensitivity, and reproducibility.<sup>20</sup> They include: (1) in vivo pharmacokinetic studies, (2) in vivo pharmacodynamic effect studies, (3) clinical endpoint studies, and (4) in vitro studies.<sup>21</sup> In addition, consistent with section 505(j)(8)(C) of the FD&C Act, section 320.24(b)(6) of the regulation states that FDA has the authority to use "[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence."<sup>22</sup> For some drug products, adequate methods for demonstrating bioequivalence have not yet been developed. In such cases, FDA will not approve an ANDA.

If FDA determines that in vivo data is the appropriate means of demonstrating bioequivalence for a product or product class, 21 CFR 320.21(f) provides that applicants may apply for a waiver of the in vivo requirement consistent with section 320.22.<sup>23</sup> Section 320.22 in turn directs that FDA "must" waive that in vivo requirement upon a subsequent showing that the individual applicant's product meets certain additional criteria.<sup>24</sup> For example, if FDA requires in vivo data for a parenteral solution intended solely for administration by injection, or for an ophthalmic or otic solution, FDA must waive that requirement if the ANDA applicant demonstrates that its individual product from that product class contains the same active and inactive ingredients in the same concentration as the RLD.<sup>25</sup> Even in instances in which such additional criteria are met, however, FDA may require in vivo data if the Agency determines that any differences between the drug product and the RLD may affect the bioequivalence of the drug product.<sup>26</sup> Section 320.22 also provides that FDA "may" waive any Agency-imposed in vivo bioequivalence data requirement for a particular product "for good cause . . . if waiver is compatible with the protection of the public health," underscoring FDA's

<sup>19</sup> 21 CFR 320.24(a).

<sup>20</sup> As discussed in detail in section I.C. below, this descending order of methodologies is not applicable to many locally acting drug products due to characteristics of those products that differ from most systemically acting drug products.

<sup>21</sup> 21 CFR 320.24(b).

<sup>22</sup> *Id.* See also *Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d 10, 20 (D.D.C. 2009) (quoting 21 CFR 320.24(b) in upholding FDA sameness determination of generic drug product).

<sup>23</sup> 21 CFR 320.21(f) ("Information to permit FDA to waive the submission of evidence measuring the in vivo bioavailability or demonstrating the in vivo bioequivalence shall meet the criteria set forth in 320.22").

<sup>24</sup> 21 CFR 320.22(a).

<sup>25</sup> 21 CFR 320.22(b)(1). See, generally, 21 CFR 320.22(b)-(d) (additional categories of products for which waivers of an in vivo data requirement may be sought).

<sup>26</sup> 21 CFR 320.22(f).

discretion to determine the most appropriate bioequivalence methodology for each product.<sup>27</sup>

The Agency's authority to make bioequivalence determinations on a case-by-case basis using in vivo, in vitro, or both types of data enables FDA to effectuate several long-recognized policies that protect the public health: (1) refraining from unnecessary human research when other methods of demonstrating bioequivalence meet the statutory and regulatory standards;<sup>28</sup> (2) permitting the Agency to utilize the latest scientific advances in approving drug products;<sup>29</sup> (3) protecting the public by ensuring only safe and effective generic drugs are approved for marketing;<sup>30</sup> and (4) making more safe and effective generic drugs available.<sup>31</sup>

### C. General Scientific Principles of Bioequivalence

For systemically acting drug products, the rate and extent of systemic absorption of the drug is usually the most sensitive, accurate, and reliable indicator of the rate and extent to which the active ingredient becomes available at the site of drug action. The determination of bioequivalence of drug products whose primary mechanism of action depends on systemic absorption generally rests on a comparison of drug and/or metabolite concentrations in an accessible biologic fluid, such as blood or urine, after administration of a single dose or multiple doses of each drug product to healthy volunteers.<sup>32</sup>

<sup>27</sup> 21 CFR 320.22(e). FDA also has the general discretion to waive any requirement set forth in subpart C of part 314, which sets forth the approval scheme for ANDAs. 21 CFR 314.99(b) ("An applicant may ask FDA to waive under this section any requirement that applies to the applicant under 314.92 through 314.99. The applicant shall comply with the requirements for a waiver under 314.90"). As FDA noted with respect to the analogous section 314.90, such waivers are intended "to give applicants the flexibility to seek alternative ways of complying with the regulatory requirements for drug approval." *New Drug and Antibiotic Regulations*, 50 FR 7452, 7490 (Feb. 22, 1985).

<sup>28</sup> 21 CFR 320.25(a) ("guiding principle" that "that no unnecessary human research should be done" expressed in regulation addressing conduct of an in vivo bioavailability study); *Abbreviated New Drug Application Regulations, Proposed Rule*, 54 FR 28872, 28883 (July 10, 1989) (in discussing section 320.22, states "the agency does not believe that Congress intended that unnecessary human research be conducted ... if the agency concludes that bioequivalence can be demonstrated by in vitro tests").

<sup>29</sup> *Bioavailability and Bioequivalence Requirements: Procedures for Establishing a Bioequivalence Requirement*, 42 FR 1624, 1629 (Jan. 7, 1977) (in promulgating final bioequivalence regulations, FDA noted that "[a]s with all new regulations relating to an evolving science, the Commissioner reserves the right to consider other factors that may indicate the need to establish a bioequivalence requirement").

<sup>30</sup> *Schering Corp. v. Sullivan*, 782 F. Supp. 645, 650 (D.D.C. 1992), (citing as one underlying policy of the Hatch-Waxman Amendments, to "ensure the safety of these drugs before they are substituted for their name-brand counterparts").

<sup>31</sup> *Id.* (Purposes of Hatch-Waxman Amendments are "to make more inexpensive generic drugs available" and "to ensure the safety of these drugs"); *Fisons Corp. v. Shalala*, 860 F. Supp. 859, 866-67 (D.D.C. 1994) (bioequivalence waiver provision "comports with the structure and broader policy objectives of the Hatch-Waxman Act" including making safe and affordable generic drugs available).

<sup>32</sup> Section 505(j)(8)(B) of the FD&C Act; guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products -- General Considerations*, at 6 (Mar. 2003) (BA/BE Guidance).

By contrast, a traditional in vivo bioequivalence study comparing rate and extent of absorption of the active ingredient into the bloodstream is of limited utility for locally acting, nonsystemically absorbed drug products such as vancomycin capsules. Rather, for locally acting, nonsystemically absorbed drug products, a showing that the active or therapeutic ingredient in the proposed generic drug reaches the site of action at a rate and extent that is not significantly different from that of the RLD, along with satisfaction of other requirements for an ANDA, generally will permit FDA to conclude that the proposed generic drug can be expected to behave the same way in the body as the RLD.<sup>33</sup>

The choice of appropriate bioequivalence study design is based on the ability of the study to compare the drug delivered by the two products at the particular site of action of the drug, and Congress assigned this decision to FDA. Congress intended to grant FDA wide discretion to establish bioequivalence standards on a drug-by-drug basis when it enacted the Hatch-Waxman Amendments,<sup>34</sup> and courts that have considered FDA's bioequivalence determinations consistently have upheld FDA's scientific discretion to determine how the bioequivalence requirement should be met for a given product or class of products.<sup>35</sup>

#### D. Development of FDA's Current Bioequivalence Recommendations for Generic Vancomycin

##### 1. Original Approval of Vancomycin Capsules

Vancomycin in some form has been used for the systemic treatment of *resistant staphylococcal infections* since the 1950s.<sup>36</sup> In 1958, FDA approved an NDA submitted by Lilly Research Laboratories (Lilly) for Vancocin Injection.<sup>37</sup> The Agency approved

<sup>33</sup> Section 505(j)(8)(C) of the FD&C Act.

<sup>34</sup> *Bristol-Myers Squibb v. Shalala*, 923 F. Supp. 212, 217 (D.D.C. 1996) ("the expressed desire of Congress, through the 1984 amendments, was that FDA retain its historically wide discretion in defining showings of bioequivalence") (internal citation and quotation omitted); *Schering Corp. v. FDA*, 51 F.3d at 399 ("there is no evidence that Congress intended to limit the discretion of the FDA in determining when drugs were bioequivalent for the purposes of ANDA approval").

<sup>35</sup> *Schering Corp. v. FDA*, 51 F.3d at 397-400 (3rd Cir. 1995); *Schering Corp. v. Sullivan*, 782 F. Supp. at 651 (deference afforded Agency's determination so long as it is not contrary to the governing statute and regulations and is based on a "reasonable and scientifically supported criterion"); *Fisons Corp v. Shalala*, 860 F. Supp. at 866-67 (D.D.C. 1994) ("[T]he factual determination of how bioequivalence is determined properly rests within the FDA's discretion."); *Astellas Pharma US, Inc. v. FDA*, 642 F. Supp. 2d at 19 (the "high degree of deference" given to FDA's scientific determinations "has been applied to the FDA's determinations regarding which methodologies it determines are needed to test the bioequivalency of a given generic").

<sup>36</sup> Lucas, R.A., Bowtle, W.J., Ryden, R. "Disposition of Vancomycin in Healthy Volunteers From Oral Solution and Semi-Solid Matrix Capsules." *J. Clin. Pharm. Ther.* 1987; 12:27-31.

<sup>37</sup> National Academy of Sciences-National Research Council Drug Efficacy Study, Log No. 1828 (Vancocin HCl Vancomycin Hydrochloride Ampules USP) (original approval Oct. 23, 1958); see also Vancomycin HCl Injection, NDA 60-180. Drugs@FDA, available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>.

an amendment to the NDA for the marketing of Vancocin Solution for oral use in 1972,<sup>38</sup> and a new indication for this solution product for the treatment of *pseudomembranous colitis* produced by CDAD in 1983.<sup>39</sup>

Lilly filed a new NDA for Vancocin Capsules<sup>40</sup> in 1985 for the treatment of SAE and CDAD.<sup>41</sup> NDA applicants must demonstrate the in vivo bioavailability of the drug, or an appropriate basis for waiver of that requirement.<sup>42</sup> Bioavailability is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.<sup>43</sup> On review of Lilly's application, FDA concluded that it could not assess systemic bioavailability of vancomycin HCl capsules from the in vivo bioavailability data Lilly had submitted because of low absorption of the capsule product. The Agency therefore permitted waiver of the in vivo bioavailability data requirement under 21 CFR 320.22(b)(3), which at that time permitted waiver of the bioavailability requirement for oral dosage forms not intended to be absorbed systemically.<sup>44</sup> In the course of its review, the Agency also concluded that the drug dissolved adequately to reach the targeted microorganisms in the GI tract.<sup>45</sup> FDA approved the capsule NDA in 1986.<sup>46</sup> ViroPharma licensed Vancocin Capsules from Lilly in 2004. The Vancocin oral solution product was withdrawn from the market in 2004, leaving the oral capsule product the only finished product for oral administration.<sup>47</sup>

The Vancocin oral capsule is the only RLD for vancomycin capsules. Therefore, any ANDA for generic vancomycin HCl oral capsules must establish bioequivalence to Vancocin to gain approval.

<sup>38</sup> Summary Basis of Approval, NDA 61-667, Vancocin for Intravenous Injection, Food and Drug Administration, Division of Freedom of Information (HFI-35), Office of Shared Services, Office of Public Information and Library Services, 5600 Fishers Lane, Rockville, MD 20857.

<sup>39</sup> Vancocin Oral Solution ANDA 61667. Drugs@FDA, available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>.

<sup>40</sup> In the original capsule application, the Vancocin capsules were described as "pulvules." Summary Basis of Approval for NDA 50606, Vancomycin HCl Pulvules. Food and Drug Administration, Division of Freedom of Information (HFI-35), Office of Shared Services, Office of Public Information and Library Services, 5600 Fishers Lane, Rockville, MD 20857.

<sup>41</sup> Id.

<sup>42</sup> 21 CFR 320.21.

<sup>43</sup> 21 CFR 320.1(a).

<sup>44</sup> *Bioavailability and Bioequivalence Requirements*, 42 FR at 1648.

<sup>45</sup> Summary Basis of Approval for NDA 50-606, FDA Medical Officer Review for Pulvules Vancocin HCL, at 1 (July 10, 1985) (in review of dosage form and route of administration, concluding "[d]issolution tests show that vancomycin hydrochloride is released quickly from the formulation"); FDA Pharmacokinetic Evaluation Division Review for Pulvules Vancocin HCL, at 2 (June 1, 1985) ("[t]he firm's dissolution specification for the capsule formulation is acceptable to the Division of Biopharmaceutics").

<sup>46</sup> Vancocin HCl Capsules, NDA 050606, Drug Details, Drugs@FDA, available at: [http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label\\_ApprovalHistory](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory).

<sup>47</sup> Drugs@FDA, Vancomycin Hydrochloride Oral Solution (indicating discontinued status) (ANDA No. 061667), available at <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails>.

2. FDA's Initial Recommendation of In Vivo Studies with Clinical Endpoints to Establish Bioequivalence for Vancomycin Capsules

FDA's initial recommendation for sponsors to establish bioequivalence to vancomycin capsules was to conduct in vivo studies with clinical endpoints. After oral administration, a vancomycin capsule releases the drug in the stomach and upper GI tract. The released drug completely dissolves in GI fluids, and then is transported along with GI fluids to its site of action in the lower GI tract.<sup>48</sup> The Clinical Pharmacology section of the approved product labeling for Vancocin describes vancomycin as poorly absorbed after oral administration.<sup>49</sup> Thus, plasma and urine concentrations of vancomycin are generally undetectable following oral administration, and traditional bioequivalence studies with pharmacokinetic (PK) measurements of such concentrations are of limited utility.<sup>50</sup> Until 2006, FDA recommended that generic applicants for vancomycin capsules submit an in vivo bioequivalence clinical endpoint study in lieu of in vivo PK measurements to demonstrate bioequivalence of generic vancomycin. In accordance with Agency practice at that time, FDA provided this in vivo clinical study bioequivalence recommendation in letters to members of the public upon request.<sup>51</sup>

3. FDA's 2006 Amendment of the Vancomycin Recommendation to Accept In Vitro Data to Establish Bioequivalence

In 2006, the Agency changed its bioequivalence recommendation for vancomycin capsules, permitting applicants to establish bioequivalence with certain in vitro dissolution studies in lieu of in vivo data. This change resulted from the Agency's evaluation of evolving scientific knowledge regarding the circumstances under which bioequivalence for certain classes of drug products may be established using in vitro dissolution data.

In August 2000, FDA had issued guidance setting forth a biopharmaceutics classification system for the waiver of in vivo data otherwise required by the Agency to demonstrate bioequivalence for immediate release (IR) solid oral dosage forms (the BCS Guidance).<sup>52</sup> For such dosage forms, differences in the bioavailability of two products (i.e., differences in the rate and extent of absorption of a drug from two solid dosage products of those products in vivo) are caused by differences in dissolution.<sup>53</sup> Bioavailability at the site of action also can be affected by the drug product's solubility (extent to which the drug substance can be dissolved in a set amount of liquid) and permeability (proportional to the rate at which a drug substance is absorbed across the intestinal membrane). In its

<sup>48</sup> Draft Vancomycin BE Guidance at 2.

<sup>49</sup> Vancocin PI at 9.

<sup>50</sup> Draft Vancomycin BE Guidance at 3.

<sup>51</sup> See, e.g., Letter fr. R. Patnaik, Ph.D., Acting Dir. OGD BE Div. (Dec. 17, 1996) (in response to letter inquiry, setting forth in vivo study requirement to demonstrate bioequivalence for vancomycin capsules).

<sup>52</sup> Guidance for industry on *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System* (Aug. 2000).

<sup>53</sup> Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R. "A Theoretical Basis for a Biopharmaceutical Drug Classification: The Correlation of In Vitro Drug Product Dissolution and In Vivo Bioavailability." *Pharm. Res* 1995, 12:413-20.

scientific judgment, FDA concluded that if an RLD is a rapidly dissolving,<sup>54</sup> highly soluble<sup>55</sup> and highly permeable<sup>56</sup> IR dosage form, demonstration of rapid in vitro dissolution of a proposed generic IR solid dosage form under appropriate dissolution criteria should provide sufficient assurance of rapid in vivo dissolution, thereby ensuring the same bioavailability as (and thus bioequivalence to) the RLD.<sup>57</sup> Such products were described as “Class I” products in the guidance.<sup>58</sup> Based on these principles, the BCS Guidance explained how a Class I product could qualify for a waiver of a requirement for in vivo data, under section 320.22(e) of FDA’s regulations. The guidance did not expressly address locally acting oral drug products like vancomycin, nor did the guidance set forth the exclusive pathway to demonstrating bioequivalence through in vitro data. Rather, it outlined certain baseline scenarios in which the Agency concluded that in vitro data could be sufficient to establish bioequivalence and that a waiver of in vivo data that FDA otherwise required would be appropriate.

Shortly after publishing the BCS Guidance, FDA issued a draft guidance entitled *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products -- General Considerations* in response to a growing number of ANDA submissions and requests for bioequivalence recommendations for specific products.<sup>59</sup> In that guidance, FDA discussed 21 CFR 320.24(b), which, as detailed above, sets out the hierarchy of generally preferred methodologies for demonstrating bioequivalence for most drug products. The Agency noted that comparative clinical studies generally are disfavored for orally administered drugs. Such trials “[are] generally considered insensitive and [should] be avoided where possible (21 CFR 320.24).”<sup>60</sup> Although the guidance primarily concerned systemically acting oral drug products, it noted that bioequivalence for orally administered drugs intended for local action in the GI tract “can be achieved using bioequivalence studies with clinical efficacy and safety endpoints and/or suitably designed and validated in vitro studies, if the latter studies are either reflective of important clinical effects or are more sensitive to changes in product performance compared to a clinical study.”<sup>61</sup>

<sup>54</sup> The BCS Guidance provides that an IR drug product is considered rapidly dissolving “when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes, using *U.S. Pharmacopeia* (USP) Apparatus at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 ml or less” in three different media (BCS Guidance at 2-3).

<sup>55</sup> An IR drug product is considered highly soluble under the BCS Guidance “when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5.” *Id.* at 2.

<sup>56</sup> An IR drug product is considered highly permeable under the BCS Guidance “when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.” *Id.* at 2.

<sup>57</sup> The BCS Guidance was premised on the well-established pharmacology principle that for a drug to become available at the site of action, it must first dissolve into solution. *Id.* at 2.

<sup>58</sup> *Id.* at 1.

<sup>59</sup> Draft guidance for industry on *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products -- General Considerations* (Oct. 2000). The guidance was finalized in 2003 (the *BA/BE Guidance* (see n. 29)).

<sup>60</sup> *Id.* at 9-10.

<sup>61</sup> *Id.* at 20.

During this time period, FDA's expert advisory committees were also considering in vitro methodologies for establishing bioequivalence. At a March 2003 meeting, FDA's Advisory Committee for Pharmaceutical Science (ACPS) considered the issue of bioequivalence for locally acting drug products applied topically to treat diseases or conditions of the skin. At that meeting, Dr. Dena Hixon, then Associate Director for Medical Affairs in FDA's Office of Generic Drugs (OGD), noted that at that time most locally acting drugs required clinical endpoint studies to demonstrate bioequivalence.<sup>62</sup> Dr. Hixon then outlined challenges that the Agency faced with clinical endpoint studies, including increased variability compared to pharmacokinetic endpoints, longer study duration, endpoint study cost, safety concerns related to the patient population, and lack of consistency between studies.<sup>63</sup> In October 2004, FDA asked the ACPS specifically to consider when dissolution testing could be used to establish bioequivalence for locally acting GI drugs. The Committee considered a range of products, and discussed whether dissolution testing, along with PK studies for some drug products that demonstrated certain levels of permeability, could be acceptable to establish bioequivalence for locally acting GI products, but the Committee did not vote on any recommendations.<sup>64</sup>

After the 2004 ACPS meeting, a generic applicant for vancomycin capsules submitted in vitro data that purported to show that vancomycin is "rapidly dissolving" under the BCS Guidance definition thereby justifying waiver of the in vivo clinical data requirement in place at that time.<sup>65</sup> FDA conducted a separate analysis to confirm that vancomycin is highly soluble, but did not independently assess the ANDA applicant's dissolution data.<sup>66</sup> On consideration of the ACPS's discussions regarding scientific developments on in vitro dissolution data,<sup>67</sup> developments in the greater scientific community regarding in vitro

<sup>62</sup> Tr. of Mar. 13, 2003, Meeting of FDA Advisory Committee for Pharm. Sci. (2003 ACPS Tr.), at 189.

<sup>63</sup> Id. at 189-93.

<sup>64</sup> See, e.g., Tr. of Oct. 20, 2004, Meeting of FDA Advisory Committee for Pharm. Sci. (2004 ACPS Tr.), at 289, 295, 336-37. You claim that the Committee's Final Report of the meeting, which states that "[i]n conclusion, the Committee agreed it was difficult to reach a consensus, but that in order to provide bioequivalence in vitro dissolution along with pharmacokinetics should be acceptable" (Summary Minutes of ACPS October 19-20, 2004, Meeting, at 6 (Nov. 16, 2004)) is not accurate because the Advisory Committee did not formally vote to endorse in vitro testing for any particular local GI drug or class of GI drugs at the 2004 meeting. VP May 17, 2007 Supp., at 7; VP Dec. 30, 2007, Supp. at 7; VP Mar. 18, 2009, Comments to Draft Guidance Docket No. 2008-D-0626 (VP Draft Guidance Resp.) at 21. You are correct that the Committee did not formally "agree" because it did not vote on the appropriate methodology, but you have not demonstrated that this summary of the proceedings (or an FDA employee's subsequent reference to this summary, VP Draft Guidance Resp. at 24) has, as you assert, compromised the Committee's subsequent consideration of appropriate bioequivalence standards for locally acting oral dosage forms including vancomycin (VP Draft Guidance Resp. at 21).

<sup>65</sup> Vancomycin is not highly permeable, and therefore does not fall directly within the BCS Guidance classification of drugs for which a waiver of in vivo data could be requested. However, for drugs that act locally in the GI tract such as vancomycin, it is the poor permeability that generally assures no loss of bioavailability at the site of action due to absorption. For this reason, such drugs may be appropriate for in vitro dissolution testing under certain circumstances even though they are not Class I drugs as described in the BCS Guidance.

<sup>66</sup> CDER Division of Product Quality Research (DPQR) 2008 Vancomycin Solubility Study (Feb. 5, 2008) (DPQR 2008 Solubility Study).

<sup>67</sup> See note 64, above.

dissolution methodologies,<sup>68</sup> the dissolution data submitted by the generic applicant, and data showing that vancomycin HCl is “highly soluble” under BCS standards, FDA revised its generic vancomycin bioequivalence recommendation in February 2006. The revised recommendation (2006 Revised Recommendation) stated that “[v]ancomycin is a highly soluble drug and the reference listed drug (RLD) product is rapidly dissolving. Waivers of in vivo bioequivalence testing can be requested in [ANDAs], provided that the test product is rapidly dissolving at the conditions specified in the [BCS guidance].”<sup>69</sup> The 2006 Revised Recommendation noted that FDA had concluded that such testing would be more sensitive than clinical trials in detecting differences in product performance. In addition, the recommendation delineated the specific dissolution data recommended to demonstrate bioequivalence.<sup>70</sup> FDA provided the 2006 Revised Recommendation in individual letters to at least 16 parties, including multiple pharmaceutical companies that had requested information related to bioequivalence recommendations for generic vancomycin.<sup>71</sup>

#### 4. ViroPharma’s 2006 Petition for Stay of Action

On March 17, 2006, you filed a petition for stay of approval of any ANDAs for generic vancomycin capsules on behalf of ViroPharma.<sup>72</sup> Specifically, you requested that the Agency:

- (a) Require ANDA applicants for vancomycin capsules to use the most rigorous scientific method that will demonstrate a rate and extent of drug release to the site of action consistent with good medicine and science;
- (b) Require ANDA applicants for vancomycin capsules to demonstrate that the stability of a vancomycin capsule ANDA product is at least as good as that of Vancocin;
- (c) Require any ANDA applicant relying on Vancocin to provide evidence that its product is bioequivalent to Vancocin along the entire gastrointestinal tract;
- (d) Convene a joint meeting of the ACPS and the Advisory Committee for Anti-infective Drug Products, with industry participation, to examine the relevant data and information related to vancomycin delivery to the GI tract for the purpose of developing appropriate and consistent standards for the approval of new vancomycin capsule products;

<sup>68</sup> See also note 86, below, for additional detail on the scientific community’s developments regarding use of dissolution data to demonstrate bioequivalence.

<sup>69</sup> See, e.g. Letter fr. D. Conner, Director, Div. Bioequivalence, CDER Office of Generic Drugs to Dr. B. Leung, Infinum Capitol Corp. (Mar. 1, 2006), attached as Ex. 1 to VP May 31, 2006, Supp.

<sup>70</sup> Id.

<sup>71</sup> FDA had distributed its previous recommendation of a clinical endpoint study methodology in the same manner. As discussed in section II.C.8(a), below, in 2007 FDA changed this “individual letter” practice of distributing bioequivalence recommendations for specific products to a process by which such recommendations generally are issued publicly as draft guidances.

<sup>72</sup> VP Petition for Stay of Action, at 1 (Mar. 17, 2006). You amended the petition on March 30, 2006, again requesting a stay of any vancomycin ANDA or 505(b)(2) approval on the ground that the Agency had not established and applied appropriate standards for approving these vancomycin applications. VP Amended Petition for Stay of Action, at 1 (Mar. 30, 2006) (VP Am. Pet.)

- (e) Validate with both the FDA Medical Policy Coordinating Committee and the FDA Biopharmaceutics Coordinating Committee the scientific and medical appropriateness of the approval standards for a new locally acting vancomycin capsule product; and
- (f) Provide an opportunity for public review and comment on the appropriate approval standards for a new locally acting vancomycin capsule product.

(VP Am. Pet. at 1-2.)

Shortly thereafter you supplemented your petition to include data that you asserted demonstrated that Vancocin is not rapidly dissolving.<sup>73</sup>

In response to your petition, FDA commissioned a study by FDA's Division of Product Quality Research (DPQR) within the Center for Drug Evaluation and Research (CDER) to determine the dissolution characteristics of Vancocin Capsules.<sup>74</sup> DPQR completed the study in February 2008, and concluded that Vancocin Capsules dissolved at a rate faster than 85% in 45 minutes at a range of predetermined pH conditions encountered in the GI tract, with the exception of two lots of the RLD drug.<sup>75</sup> The study also found that Vancocin Capsules dissolved at a rate faster than 85% in 30 minutes when the pH of the dissolution media was pH 1.2,<sup>76</sup> and, with the exception of one lot, all the products were found to dissolve over 90% in 60 minutes.<sup>77</sup> The study observed that Vancocin is not "rapidly dissolving" as defined in the BCS Guidance, however, which requires 85% dissolution within 30 minutes (rather than 45) at all of the predetermined pH levels.<sup>78</sup>

FDA had also previously commissioned a DPQR study on the solubility of vancomycin under specific pH conditions that were within the extremes of normal physiological pH of the human GI tract.<sup>79</sup> As described above, under the BCS Guidance, a drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1-7.5. The high solubility boundary layer for vancomycin is based on its highest dose strength of 250 mg dissolved in 250 mL of aqueous media. Upon application of these criteria, the study found that at all BCS pH levels, Vancocin required less than 250 mL to dissolve the highest dosage strength of 250 mg.<sup>80</sup> Vancomycin therefore was confirmed to be highly soluble under BCS standards.

<sup>73</sup> VP June 30, 2006, Supp., at 36-41 (challenging bioequivalence recommendation on scientific grounds).

<sup>74</sup> DPQR 2008 Vancomycin Dissolution Study (Feb. 5, 2008) (DPQR 2008 Dissolution Study). While the study involved the examination of Vancocin capsules and of other vancomycin capsules, DPQR's conclusions with respect to the dissolution of vancomycin capsules were based only on the division's findings with respect to Vancocin (Id. at 14).

<sup>75</sup> Id. at 34.

<sup>76</sup> Id.

<sup>77</sup> Id. at 14.

<sup>78</sup> Id.

<sup>79</sup> DPQR 2008 Solubility Study.

<sup>80</sup> Id. at 17.

In July 2008, FDA convened the ACPS<sup>81</sup> to consider bioequivalence for locally acting GI drug products with low solubility. At this meeting the Committee also discussed bioequivalence for highly soluble GI oral drug products, and the use of in vitro dissolution data over the relevant pH levels to demonstrate bioequivalence for highly soluble products.<sup>82</sup> The Committee then discussed the role of excipients, or inactive ingredients, in such products, whether they can affect dissolution or drug performance, and if so, whether FDA should require a generic product seeking to use in vitro dissolution data to show bioequivalence to demonstrate that excipients in its product are qualitatively (Q1) and quantitatively (Q2) the same as the RLD.<sup>83</sup>

##### 5. FDA's 2008 Amendment to the Vancomycin Bioequivalence Recommendation

In December 2008, FDA issued the Draft Vancomycin BE Guidance. With this guidance, FDA amended the 2006 Revised Recommendation to incorporate the Agency's findings from the DPQR dissolution studies and other relevant information, including submissions to this citizen petition docket. FDA concluded that notwithstanding that vancomycin capsules are not "rapidly dissolving" under the BCS Guidance, in vitro dissolution studies still are an appropriate method of demonstrating bioequivalence for vancomycin capsules. As described in the Draft Vancomycin BE Guidance,<sup>84</sup> two key factors led FDA to this conclusion. First, vancomycin acts primarily in the colon, and GI transit times for drugs to reach the colon average 3 to 4 hours. Dissolution even at 60 minutes, which all but one Vancocin lot demonstrated in the 2008 DPQR Dissolution Study, ensures that even in patients with faster transit times than healthy subjects, vancomycin will be completely dissolved when it reaches the colon.<sup>85</sup> Second, as discussed in detail in section II.B.2(d), similar dissolution profiles across the pH ranges recommended in the bioequivalence recommendation ensure that generic and reference products will have equivalent release even in patients with extremely short GI transit times or in conditions that would not permit either the reference or the generic product to completely dissolve. FDA also considered the fact that the use of 30 minutes in the BCS scheme generally is considered to be a conservative baseline, and that the consensus among academic, industry, and regulatory scientists is that 85% dissolution at 60 minutes is sufficient to permit demonstration of bioequivalence by use of in vitro data.<sup>86</sup>

<sup>81</sup> Prior to its meeting in July 2008, the name of the ACPS was changed to the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology. For the sake of consistency, we will continue to refer to this committee as the ACPS in this response.

<sup>82</sup> See, e.g., Tr. of July 23, 2008, Meeting of FDA Advisory Committee for Pharm. Sci. (2008 ACPS Tr.), at 31-33, 36-38.

<sup>83</sup> Id. at 31, 83, 207-08.

<sup>84</sup> Draft Vancomycin BE Guidance at 2.

<sup>85</sup> See section II.B.2(g) below for a detailed discussion of this conclusion.

<sup>86</sup> Polli, J.E., Yu, L.X., Cook, J.A., Amidon, G.L., Borchardt, R.T., et al., "Summary Workshop Report: Biopharmaceutics Classification System--Implementation challenges and Extension Opportunities. *J. Pharm. Sci.* 2004; 93:1375-81 (BCS Implementation Article). As a general matter, the BCS Guidance is considered internationally to be conservative with respect to the class boundaries of solubility and permeability, and the dissolution criteria. Yu, L.X., Amidon, G.L., Polli, Z.E., Zhao, H., Mehta, M.U., Conner, D.P., Shah, V.P., Lesko, L.J., Chen, M.-L., Less, V.H.L., Hussain, A.S. "Biopharmaceutics Classification System: The Scientific Basis for Biowaiver Extensions." *Pharm. Res.* 2002;19:921-25.

The Draft Vancomycin BE Guidance details FDA's recommendation for establishing bioequivalence for generic vancomycin capsules. First, the draft guidance provides that in vitro dissolution studies may demonstrate bioequivalence for test formulations that are Q1/Q2 the same as the RLD with respect to inactive ingredients. FDA included the Q1/Q2 criterion because the Agency concluded that generic applicants might use different inactive ingredients that may affect the transport, dissolution, absorption, and/or effectiveness of the drug.<sup>87</sup> For proposed generic vancomycin products that are not Q1/Q2 the same as the RLD with respect to inactive ingredients, the draft guidance recommends in vivo bioequivalence studies with clinical endpoints, unless the ANDA sponsor can provide evidence that the differences in excipients will not affect the safety or effectiveness of the proposed generic drug product.<sup>88</sup>

The draft guidance and its accompanying *Federal Register* notice make clear that the recommended bioequivalence methodologies are not the exclusive means by which an

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In 2006 the World Health Organization (WHO) provided guidance to regulatory agencies around the world and recognized BCS-based biowaivers. WHO extended FDA's BCS-based biowaiver approach to highly soluble and poorly permeable (BCS Class III) drugs whose formulations exhibit very rapid dissolution, and to a select group of poorly soluble and highly permeable (BCS Class II) drugs that are highly soluble and rapidly dissolving at pH 6.8. In 2002 and 2007, FDA co-sponsored two scientific workshops on implementation and extensions of BCS-based biowaivers. BCS Implementation Article at 1376; Polli, J.E., Abrahamsson, B.S.I., Yu, L.X., Amidon, G.L., Baldoni, J.M., et al., Summary Workshop report: Bioequivalence, Biopharmaceutics Classification System and Beyond, *AAPS J.*, 2008;10(2):373-9 (BCS and Beyond Article). Over 400 national and international participants from government, industry, and academia attended these two workshops, signifying the importance of this dissolution-based biowaiver approach. The 2002 workshop report states "[c]onsensus held that this (rapid dissolution) definition should be broadened to include products that provide no less than 85% dissolution in 60 min." BCS Implementation Article, at 1379. The 2007 workshop report states "[a] key highlight of the workshop was the continued scientific support for biowaivers for Class III compounds whose formulations exhibit very rapid dissolution" BCS and Beyond Article, at 374.

<sup>87</sup> Draft Vancomycin BE Guidance at 1. You correctly note that FDA does not expressly cite legal authority in the draft guidance. VP Mar. 25, 2010, Supp. at 27. This does not mean that FDA lacked authority to set forth this recommendation, however. As set forth above in section I.B, FDA has clear authority to determine bioequivalence standards for specific drug products in accordance with the statute and regulations. (See section 505(j)(7)(A)(i) of the FD&C Act; see also 21 CFR 320.1(f) and 21 CFR 324). FDA cited this authority in its general guidance that describes FDA's process for issuing guidances recommending bioequivalence methodologies for specific products, which is discussed in detail below. Draft guidance for industry on *Bioequivalence Recommendations for Specific Products*, at 2 (May 2007) (citing section 505(j)(8)(C) and 21 CFR 320.24). The fact that FDA did not expressly cite its authority in the Draft Vancomycin BE Guidance does not render that authority inoperative. (Note that FDA issued the final version of this guidance in June 2010, and further citations are to the final version (Specific Product BE Guidance).

<sup>88</sup> Draft Vancomycin BE Guidance at 1. Your assertion that the 2008 draft guidance constituted a break from the consideration given to products that fall directly within the BCS Guidance is misplaced. VP Draft Guidance Resp., at 19. Far from abandoning the scientific principles that provided the foundation of the BCS Guidance, FDA used those scientific principles as a springboard to investigate and identify more sensitive, accurate and reproducible methodologies for demonstrating bioequivalence. Also contrary to your assertion (*id.*) otherwise, the draft bioequivalence recommendation for vancomycin HCl capsules was consistent with the 2004 ACPS's discussion that dissolution testing should be acceptable to establish bioequivalence for locally acting GI products, and that PK studies are not appropriate for demonstrating the bioequivalence of vancomycin capsules because its drug levels are generally not detectable in the plasma or urine due to very limited absorption. Draft Vancomycin BE Guidance at 2.

ANDA applicant could meet the statutory requirement.<sup>89</sup> As the draft guidance expressly notes, the recommendations represent the Agency's "current thinking on this topic" and "an alternative approach" may be used if such "approach satisfies the requirements of the applicable statutes and regulations."<sup>90</sup> To provide additional information to persons considering the draft guidance, the recommendations also include a significant amount of background information and set forth the Agency's scientific rationale for the in vitro and in vivo bioequivalence recommendations.<sup>91</sup>

The Agency issued the Draft Vancomycin BE Guidance under a process FDA had introduced in May 2007.<sup>92</sup> As described in FDA's Specific Product BE Guidance, FDA has disseminated product-specific bioequivalence recommendations in draft guidance form since 2007. The availability of bioequivalence recommendations for specific products is announced in the *Federal Register*. As a result, bioequivalence recommendations are disseminated more broadly than would have been possible using the previous "letter" format, in which product-specific letters only were sent to members of the public who had requested such information. This "product specific guidance" method also is intended to provide a meaningful opportunity for the public to consider and comment on those recommendations.<sup>93</sup>

ViroPharma and others requested, and FDA granted, additional time to submit comments on the Draft Vancomycin BE guidance. ViroPharma submitted its comments on March 18, 2009, and in two additional submissions.<sup>94</sup> FDA also received and carefully considered comments from a variety of parties, including generic and other innovator drug manufacturers, doctors, patients, patient advocacy groups, and concerned citizens.<sup>95</sup>

<sup>89</sup> Draft Vancomycin BE Guidance at 1.

<sup>90</sup> Id. See also availability of draft guidance on *Bioequivalence Recommendation for Vancomycin HCl*, 73 FR 76362, 76363 (Dec. 16, 2008).

<sup>91</sup> Draft Vancomycin BE Guidance, at 2-3.

<sup>92</sup> Specific Product BE Guidance. You submitted comments to the *draft* Specific Product BE Guidance on August 29, 2007. Letter fr. ViroPharma to FDA re. Draft Guidance for Industry on Bioequivalence Recommendations for Specific Products, Docket No. 2007-D-0168 (Aug. 29, 2007), attached as exhibit to VP Jan. 11, 2008, Supp., at 2.

<sup>93</sup> Specific Product BE Guidance at 1. You have requested information on the process by which FDA publishes draft guidances (VP Mar. 25, 2010, Supp. at 4). As a general matter, the Agency develops product-specific bioequivalence recommendations based on its understanding of the characteristics of the RLD, information derived from published literature, Agency research, and consultations within different offices in CDER, as needed, based upon the novelty or complexity of the bioequivalence considerations. Specific Product BE Guidance at 2-3. FDA does not, as you contend, publish product-specific guidances only when it lacks validation for the methodologies proposed therein and seeks evidence from outside sources (VP Mar. 25, 2010, Supp. at 22).

<sup>94</sup> Letter fr. ViroPharma to FDA Docket No. 2008-D-0626 (Dec. 19, 2008). Several parties opposed this request for an extension, claiming ViroPharma improperly was trying to delay approval of generic drugs. See, e.g. Feb. 2, 2009, Letter fr. M. Dotzel, Zuckerman Spaeder LLP, to FDA Docket No. 2008-D-0626, at 1. Upon consideration of the filings, FDA granted any interested party 30 additional days to file comments (Draft guidance for industry on *Bioequivalence Recommendation for Vancomycin HCl; Extension of Comment Period*, 74 FR 6640, 6640-41 (Feb. 10, 2009)). VP filed its comments on March 18, 2009. VP Draft Guidance Resp. ViroPharma submitted additional comments to the draft guidance docket on April 3, 2009, and May 18, 2009.

<sup>95</sup> See FDA Docket No. 2008-D-0626, available at <http://www.regulations.gov/search/Regs/home.html#docketDetail?R=FDA-2008-D-0626>.

6. The 2009 ACPS's Unanimous Endorsement of FDA's 2008 Vancomycin BE Recommendation

In August 2009, FDA convened the ACPS for the express purpose of considering the use of in vitro dissolution methods to establish bioequivalence for vancomycin capsule products. FDA convened this meeting to solicit external scientific expert opinion on the draft in vitro data recommendation, and to ensure that interested parties had a full opportunity to consider and comment on the proposed bioequivalence standard for generic vancomycin. The questions presented to the Committee for consideration were:

1. For potential Vancomycin HCl Capsule generic products that:

- (a) contain the same active and inactive ingredients in the same amounts as Vancocin Capsules,
- (b) meet currently accepted standards for assay, potency, purity, and stability (equivalent to those in place for Vancocin Capsules), and
- (c) are manufactured according to cGMP [current good manufacturing practices as set forth in FDA regulations]:

Do you accept the FDA recommendation to demonstrate bioequivalence through equivalent dissolution in media of pH 1.2, 4.5, and 6.8?

2. If your answer to (1) is no:

What potential difference between generic Vancomycin HCl Capsules and Vancocin Capsules is not accounted for in the FDA recommendation?

3. For potential Vancomycin HCl Capsule ANDA products that:

- (a) do not contain the same inactive ingredients in the same amounts as Vancocin Capsules,
- (b) meet currently accepted standards for assay, potency, purity, and stability, (equivalent to those in place for Vancocin Capsules), and
- (c) are manufactured according to cGMP:

Do you accept the FDA recommendation of a clinical endpoint bioequivalence study in patients to evaluate the effect of the different inactive ingredients?<sup>96</sup>

Prior to the meeting, ViroPharma submitted a letter challenging certain statements made in the background materials that had been distributed to the Committee members and the public.<sup>97</sup> ViroPharma's letter and FDA's response to the letter were provided to the

<sup>96</sup> *Questions for the Committee*, FDA Advisory Committee for Pharmaceutical Science and Clinical Pharmacology (Aug. 4, 2009), available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/UCM179396.pdf>.

<sup>97</sup> Letter fr. ViroPharma to FDA Docket No. 2009-N-0664 (July 31, 2009), at 4, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/UCM175010.pdf>.

Committee members, and were made part of the public record pertaining to the meeting before the August ACPS meeting date.<sup>98</sup>

FDA and industry representatives, including representatives of ViroPharma, presented materials at the meeting. Members of the public also had an opportunity to comment. The Committee conducted an extensive discussion of the scientific bases for the bioequivalence recommendation in the Draft Vancomycin BE Guidance, including many of the scientific concerns you have raised in your citizen petition and in comments to the draft guidance docket (discussed in detail below).

At the conclusion of the meeting, the Committee voted unanimously in favor of endorsing the bioequivalence recommendation set forth in the Draft Vancomycin BE Guidance.<sup>99</sup> Because the Committee voted unanimously on question #1, the group did not vote on question #2.<sup>100</sup> The Committee conducted a brief discussion of question #3, but FDA removed the question from a vote because the Committee did not have sufficient time to fully consider and make a recommendation on this question.<sup>101</sup>

#### 7. ViroPharma's Freedom of Information Act Requests

In March 2006, ViroPharma filed with the Agency a request under the Freedom of Information Act (FOIA)<sup>102</sup> for documents relating to the 2006 Revised Recommendation set forth in the letters sent to entities that had requested such information. ViroPharma made a second request in December 2008 for documents related to the Draft Vancomycin BE Guidance and any communications to third parties regarding the methodology set out in the Draft Vancomycin BE Guidance prior to December 15, 2008. FDA produced documents responsive to these requests on March 20 and October 28, 2009, and supplemented this production on December 9, 2009, February 24, 2010, and April 22,

<sup>98</sup> Id. at 1-3.

<sup>99</sup> Tr. of Aug. 4, 2009, Meeting of FDA ACPS (2009 ACPS Tr.), at 383-392.

<sup>100</sup> You erroneously contend that the August 2009 Advisory Committee proceedings were tainted by a discussion of the high costs of Vancocin and of bioequivalence studies with clinical endpoints, and that as a result, the Committee's endorsement of the in vitro dissolution data pathway is not reliable. VP Oct. 6, 2009, Supp. at 10-11. It is neither surprising nor inappropriate that the Committee discussed the lower cost of generic vancomycin. The potential benefit to consumers through increased competition in the drug industry is a primary purpose of the Hatch-Waxman Amendments. *Teva Pharm. Indus. v. Crawford*, 410 F.3d 51, 55 (D.C. Cir. 2005) ("Congress sought to strike a balance between incentives, on one hand, for innovation, and on the other, for quickly getting lower-cost generic drugs to market"); *Mead Johnson Pharm. Group v. Bowen*, 838 F.2d at 1332, 1333 (D.C. Cir. 1988). More broadly, courts have long recognized that "a primary purpose" of the FD&C Act is the protection of the "ultimate consumer's economic interest." *U.S. v. Article Consisting of 216 Cartoned Bottles*, 409 F.2d 734, 740 (2d Cir. 1969). See also n. 31, supra. Discussion of these policies during a committee meeting considering generic drug approval was not improper. There also is clear indication that the Committee members differentiated between cost concerns and the scientific questions related to the appropriate bioequivalence standard. See, e.g., 2009 ACPS Tr., at 219 (comment by Committee member Harriet B. Nembhard, Ph.D.) ("I appreciated the case made in terms of clinical practice and price and duplicating suppliers and so forth. But in terms of the bioequivalence, the innovator makes a case for addressing Q3 in the standards. I find that's an interesting idea but I'm not sure the case was fully made").

<sup>101</sup> 2009 ACPS Tr. at 393-411.

<sup>102</sup> Freedom of Information Act of 1966, Pub.L. 89-554, 80 Stat. 378.

2010. ViroPharma and FDA disagreed on several matters related to the Agency's production. ViroPharma sued FDA on December 16, 2008, alleging unlawful withholding of Agency records.<sup>103</sup> The parties filed cross-motions for summary judgment, and on March 16, 2012, the court granted in part and denied in part FDA's motion for summary judgment, and denied ViroPharma's motions for summary judgment and in camera review (judicial review of the documents that FDA withheld from production due to a claim of privilege). The court also directed the Agency to further explain the Agency's reasons for withholding certain documents.<sup>104</sup> To the extent that any issues you raise in your petition or supplements concern these FOIA requests and/or the adequacy of FDA's production,<sup>105</sup> the Agency declines to address those issues in this response due to the pending civil action.

## II. DISCUSSION

### A. FDA's Recommended Methodology for Demonstrating Bioequivalence for Vancomycin Capsules Is the Most Accurate, Sensitive, and Reproducible Approach Available

The fundamental question raised by your petition is whether the bioequivalence recommendation set forth in the Draft Vancomycin BE Guidance and unanimously endorsed by the ACPS in August 2009, is the most accurate, sensitive, and reproducible approach available among those set forth in 21 CFR 320.24(b), thereby permitting the approval of an ANDA that applies FDA's recommendation. Upon consideration of the foregoing history, the materials filed in the dockets for this citizen petition and the Draft Vancomycin BE Guidance, the discussion and unanimous endorsement of the August 4, 2009, ACPS that directly considered bioequivalence for vancomycin capsules, and the relevant scientific and legal authorities, FDA concludes for the reasons set forth below that your scientific challenges to the recommended bioequivalence methodology set forth in the Draft Vancomycin BE Guidance are unsupported, and that the recommendation is the most accurate, sensitive, and reproducible approach for demonstrating bioequivalence of generic vancomycin capsules.

<sup>103</sup> Complaint at ¶ 40-43, *ViroPharma Inc. v. U.S. Dept. of Health and Human Services*, Civil Action No. 08-2189 (D.D.C., filed Dec. 16, 2008) (Friedman, J.).

<sup>104</sup> Order, at 1, *ViroPharma Inc. v. U.S. Dept. of Health and Human Services*, Civil Action No. 08-2189 (D.D.C. Mar. 16, 2012).

<sup>105</sup> See, e.g. VP Jan. 15, 2010, Supp. at 6 (requesting that FDA confirm no responsive documents to ViroPharma FOIA request), 28-29; VP Mar. 25, 2010, Supp. at 1-2, 12-15.

## 1. FDA's 2008 Recommended Bioequivalence Methodology

The Draft Vancomycin BE Guidance is set forth in full directly below:

*Contains Nonbinding Recommendations*

**Draft Guidance on Vancomycin Hydrochloride**

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the Office of Generic Drugs.

**Active ingredient:** Vancomycin Hydrochloride

**Form/Route:** Capsules/Oral

**Recommended studies:** 2 Options: *In Vitro* or *In Vivo* Studies

1. **In Vitro Option:**

If the test product formulations are qualitatively (Q1) (i.e., contain all of the same inactive ingredients) and quantitatively (Q2) the same as the reference listed drug (RLD) with respect to inactive ingredients, bioequivalence (BE) of all capsule strengths may be established based on comparative dissolution.

For test product formulations that are Q1 and Q2 the same as the RLD, dissolution data in each specified medium should be provided for 12 capsules each of test and reference products, as follows:

**Apparatus:** USP

**Apparatus 1 (basket) Rotation speed:** 100 rpm

**Medium:** 0.1N HCl (or 0.1N HCl with NaCl at pH 1.2), pH 4.5 Acetate buffer, and pH 6.8 Phosphate buffer

**Volume:** 900 mL **Temperature:** 37°C

**Sample times:** 5, 10, 20, 30, and 45 minutes or as needed for profile comparison

An  $f_2^{1[106]}$  test should be performed using mean profiles to ensure comparable test (T) and reference (R) product drug release under a range of pH conditions. The  $f_2$  test comparing T vs. R in each medium should be between 50 and 100.

<sup>106</sup> Dissolution profiles may be compared using the following equation that defines a similarity factor ( $f_2$ ):  

$$f_2 = 50 \text{ LOG } \{ [1 + 1/n \sum^n (R - T)^2]^{-0.5} \times 100 \}$$

## 2. In Vivo Option

If the test product formulations are not Q1 and Q2 the same as the RLD with respect to inactive ingredients, BE should be established by conducting an in vivo study with clinical endpoints in patients with *Clostridium difficile* Associated Diarrhea (CDAD). We recommend that any sponsor choosing this option submit their protocol to the OGD clinical review team for review and concurrence prior to initiating the study.

### **Dissolution testing for stability and quality control:**

USP Method

### **Scientific Rationale for In Vitro and In Vivo BE Recommendations**

1. Vancomycin HCl Capsules are administered orally for treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains) and antibiotic-associated pseudomembranous colitis caused by *C. difficile*. Vancomycin HCl is poorly absorbed after oral administration. During multiple dosing of 250 mg every 8 hours for 7 doses, no blood concentrations were detected and urinary recovery did not exceed 0.76%. Orally administered vancomycin does not usually enter the systemic circulation even when inflammatory lesions are present.<sup>2[107]</sup>
2. Vancomycin acts locally in the lower gastrointestinal (GI) tract. After oral administration, a vancomycin capsule releases the drug in the stomach and upper GI tract, the released drug is completely solubilized in GI fluids, and is transported along with GI fluids to its site of action in the lower GI tract. The BE of two capsule formulations of oral vancomycin HCl is determined by the following factors:
  - Equivalent release of vancomycin from the two capsule formulations,
  - The high solubility of vancomycin drug substance,
  - The effect of inactive ingredients on the transport of vancomycin drug through the GI tract and/or the effectiveness of drug at the site of action

FDA's BE recommendation includes evaluation of all of these factors and is supported by FDA laboratory investigations.

3. The FDA laboratory conducted solubility studies at physiologically relevant pH ranges (**attached**). The results demonstrate that vancomycin HCl is highly

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where  $R_t$  and  $T_t$  are the percent dissolved at each time point. An  $f_2$  value between 50 and 100 suggests the two dissolution profiles are similar. See Guidance for Industry *Immediate Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995), at 23

<sup>107</sup> Approved label for Vancocin® HCl Capsules, USP ©, 2005, ViroPharma Inc., Exton, PA, 19431.

soluble over the physiologically relevant pH range of 1.0 to 7.5. Vancomycin HCl at pH 1, 3, 4, 5 and 7.5 would require 1.78, 1.27, 83.8, 26.3 and 14.2 ml of aqueous media, respectively, to dissolve the highest dose strength of 250 mg of vancomycin HCl.

4. The FDA laboratory conducted dissolution studies in physiologically relevant dissolution media at pH 1.0, 4.5, and 6.8 buffers (attached). The data show that the reference vancomycin HCl capsules (Vancocin) will generally dissolve more than 85% in 30 minutes at pH 1.0, in 45 minutes at pH 4.5, and in 60 minutes at pH 6.8. Given that vancomycin is highly soluble at pH conditions encountered in the GI tract,<sup>3[108]</sup> and the dosage form is expected to be in contact with a relatively large fluid volume,<sup>4[109]</sup> vancomycin is expected to be in solution long (e.g., hours) before it reaches the site of action in the lower GI tract.<sup>5[110]</sup> FDA's BE recommendation recognizes that the patient population may have variability in GI pH or transit times and thus requests that the test and reference products demonstrate similar ( $f_2 > 50$ ) dissolution profiles over a range of relevant pH conditions. Similar dissolution profiles ensure that test and reference products will be equivalent even in patients with relatively short GI transit times.
5. Inactive ingredients in oral formulations may affect the transport of drug through the GI tract and/or the effectiveness of drug at the site of action. To ensure that differences in inactive ingredients will not affect the safety and effectiveness of generic vancomycin HCl oral capsules, we recommend a BE study with clinical endpoints for test products that are not Q1 and Q2 the same relative to the RLD with respect to inactive ingredients unless the ANDA sponsor provides evidence that the differences in excipients will not affect the safety or efficacy of the proposed generic drug product.

### BE Recommendation History

As set forth in the Clinical Pharmacology section of the approved product labeling for Vancocin Oral Capsules, the RLD to which generic vancomycin HCl must be demonstrated to be BE, vancomycin is poorly absorbed after oral administration and does not usually enter the systemic circulation. Thus, plasma and urine concentrations of vancomycin are generally undetectable following oral administration, and traditional BE studies with pharmacokinetic (PK) measurements are of limited utility. Accordingly, in 1996, FDA recommended an in vivo BE study with clinical endpoints in patients to demonstrate BE of generic vancomycin HCl oral capsules.

<sup>108</sup> The pH range in the GI tract under fasted conditions is 1.5 to 2.5 in the stomach, 5.0 to 6.0 in the duodenum, 6.0 to 7.0 in the jejunum, and 7.5 in the ileum. See Willmann, S., Schmitt, W., Keldenich, J., et al. *J Med Chem.* 47: 4022-4031 (2004).

<sup>109</sup> The physiological fluid volume of the small intestine varies from 500 mL (fasting conditions) to approximately 1000 mL or more (fed conditions). See Dressman, J. and Reppas, C. *Eur J Pharm Sci.* 11: S73-S80 (2000).

<sup>110</sup> The average transit time in the small intestine is 3 to 4 hours. See Davis, S., Hardy, J., and Fara, J. *Gut.* 27: 886-892 (1986).

In October 2004, FDA asked its Advisory Committee for Pharmaceutical Science to consider when dissolution testing could be used to establish BE for locally acting GI drugs. The Committee concluded that dissolution testing along with PK studies should be acceptable to establish BE for such products. In light of the Committee's conclusions, after obtaining data showing that vancomycin HCl is highly soluble at pH conditions encountered in the GI tract and expected to be in solution long before it reaches the site of action in the lower GI tract, FDA revised its recommendation in early 2006 to include in vitro dissolution studies to demonstrate BE of generic vancomycin HCl oral capsules. This approach would provide OGD with information about drug availability at the site of action and would be more sensitive than clinical trials in detecting differences in product performance. FDA provided its 2006 revised BE recommendation to those parties that had requests pending with FDA for this information. In March 2006, Viropharma, Inc., the manufacturer of the RLD Vancocin, filed a petition for stay of action (PSA), challenging FDA's revised recommendation (Docket No. FDA-2006-P-0007).<sup>5[111]</sup>

In this draft recommendation, FDA further clarifies its recommendations on the design of studies for demonstrating BE of vancomycin HCl capsules. Because, as set forth above, generic applicants may use different inactive ingredients, which may affect the transport, absorption, and/or effectiveness of the drug, FDA is currently recommending in vitro dissolution studies only for test formulations that are Q1 and Q2 the same as the RLD. For test formulations that are not Q1 and Q2 the same as the RLD with respect to inactive ingredients, FDA is recommending in vivo BE studies with clinical endpoints.

We note that the proposed recommendations for the BE evaluation of vancomycin capsules are consistent with the 2004 Advisory Committee's conclusion. PK studies are not appropriate in this case, however, because as stated above, vancomycin levels are generally not detectable in the plasma or urine due to very limited absorption.

FDA invites comments on this draft recommendation and will carefully consider such comments before responding to Viropharma's PSAs and finalizing this recommendation.

\* \* \* \* \*

#### B. ViroPharma's Scientific Challenges to the Bioequivalence Recommendation Lack Merit

You have asserted that, notwithstanding the 2009 ACPS's unanimous endorsement of this methodology, the vancomycin bioequivalence recommendation is scientifically flawed on several grounds. Upon careful review of your submissions, FDA disagrees.

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<sup>111</sup> This PSA was originally assigned docket number 2006P-0124. The number was changed to FDA-2006-P-0007 as a result of FDA's transition to its new docketing system (Regulations.gov) in January 2008. This docket also includes a second PSA and numerous supplements filed by ViroPharma.

1. Clinical Endpoint Trials Are Not the Most Sensitive Method By Which Bioequivalence Can Be Established for Vancomycin

You argue that FDA must require data from in vivo clinical endpoint studies in CDAD patients to demonstrate bioequivalence. FDA has determined, however, that clinical endpoint studies are not always the most sensitive methodology to demonstrate bioequivalence for locally acting GI products due to increased variability compared to pharmacokinetic or in vitro dissolution studies. In particular, in vivo clinical endpoint studies measure formulation differences indirectly rather than directly, include confounding variables such as different severities of disease, may have variability in the definition of the instrument used to measure efficacy (i.e., what is being used for the primary endpoint), and may have difficulty in assessing dose response (the pattern of physiological response to varied dosage). Moreover, clinical endpoint studies require a longer study duration to assess clinical endpoint(s) than the time required to complete in vitro dissolution studies, and may not be able to use the most sensitive dose because of safety concerns related to the patient population stemming from a disparity between the dosing strength that may best reveal differences in formulation and the strength that is necessary to adequately treat the disease. There also is a lack of consistency between studies that contribute to a lack of sensitivity of clinical endpoint studies for locally acting GI products.<sup>112</sup> This conclusion is consistent with the ACPS discussions of this issue.<sup>113</sup> This conclusion also is consistent with FDA's recommended bioequivalence methodology for a number of locally acting drug products, for which FDA has expressly determined that use of in vivo clinical endpoint trials to demonstrate bioequivalence is not the most sensitive method.<sup>114</sup> FDA's recognition of the shortcomings of clinical endpoint studies for orally administered drugs is underscored in the *BA/BE Guidance*, in which the Agency generally recommends that "that the use of comparative clinical trials as an approach to demonstrate [bioequivalence] generally be considered insensitive and be avoided where possible."<sup>115</sup>

<sup>112</sup> See 2008 ACPS Tr. at 42-63.

<sup>113</sup> *Id.*

<sup>114</sup> See, e.g., May 7, 2008 Letter fr. FDA to W. Rakoczy, at 7 (rejecting a request to require in vivo bioequivalence testing, concluding that "given that [the acarbose tablet] acts locally in the GI tract and is not systemically absorbed, we believe that the appropriate methodology for establishing bioequivalence may be in vitro testing [for Q1/Q2 products] or in vivo testing with a pharmacodynamic endpoint"), available at <http://www.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480552878>; Aug. 20, 2010 Letter fr. FDA to I. Hara, Warner Chilcott Co. LLC. at 11 (concluding comparative clinical endpoint studies "less sensitive, accurate and reproducible" than in vitro dissolution and pharmacokinetic studies for mesalamine, a locally acting GI product); Dec. 8, 2010 Letter fr. FDA to J. Jonas, Shire Development Inc., at 6-7 (denying request to require clinical efficacy studies to demonstrate bioequivalence for locally acting lanthanum carbonate oral chewable tablets, concluding that "comparative in vivo trials would be less sensitive, accurate or reproducible than [pharmacodynamics] or properly designed and conducted in vitro dissolution and binding studies with respect to the capability to detect product differences").

<sup>115</sup> *BA/BE Guidance* at 9.

2. The Recommended In Vitro Dissolution Study Adequately Accounts for Disease-Specific Attributes of the GI Tract

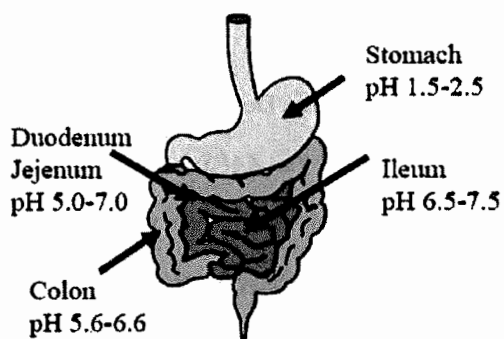
In your petition, you assert that the bioequivalence methodology set forth in the Draft Vancomycin BE Guidance is not the most sensitive, accurate, and reproducible for vancomycin because it fails to adequately take into account the disease states of CDAD and SAE patients on several grounds, and that the only methodology that is adequate is an in vivo study with clinical endpoints in patients with CDAD. FDA does not agree. Your specific points are addressed below.

(a) Background on the GI Tract of CDAD and SAE Patients

Some background on the GI tract of CDAD and SAE patients is helpful in addressing your claims. The GI tract refers to the esophagus, stomach, and intestine. The upper GI tract consists of the esophagus, stomach, and duodenum. The lower GI tract includes most of the small intestine and all of the large intestine. The small intestine has three parts: duodenum, jejunum, and ileum. The large intestine consists of cecum, colon, and rectum.

As shown in Figure 1, the mean gastric pH in healthy volunteers ranges between 1.5 and 2.5 under fasted conditions. In the intestine, there is a pH gradient, with pH values tending to rise moving down the small intestine. In the fasted state, the mean pH value in the duodenum increases from 5.0 at the pyloric sphincter to 6.0 at the distal end of the duodenum. The pH gradient in the jejunum ranges from 6.0 to 7.0, and increases further to 7.5 in the ileum.<sup>116</sup> The pH of the colon can vary, depending on bacterial activity and undigested carbohydrates, with the result that the colon pH is lower than that of the terminal ileum and is generally about pH 6.0.<sup>117</sup>

Fig 1. Stomach and Intestine pH<sup>118</sup>



<sup>116</sup> Willmann, S., Schmitt, W., Keldenich, J., Lippert, J., Dressman, J.B., "A Physiological Model for the Estimation of the Fraction Dose Absorbed in Humans." *J Med Chem* 2004;47:4022-31.

<sup>117</sup> Cummings, J.H., Pomare, E.W., Branch, W.J., Naylor, C.P.E., Macfarlane, G.T. "Short Chain Fatty Acids in Human Large Intestine, Portal, Hepatic, and Venous Blood." *Gut* 1987;28:1221-7.

<sup>118</sup> Lionberger, R, OGD Slide Presentation, at 18, Aug. 4, 2009, ACPS Meeting, <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/UCM179409.pdf>.

Table 1 below compares the gastrointestinal conditions of healthy subjects and CDAD and SAE patients at fasted state. In patients, it is possible that the pH profile may differ from that in healthy subjects. Some patients may have pH as high as 7.5.<sup>119</sup> Table 2 details vancomycin solubility at different pH levels.

Table 1. Gastrointestinal conditions of healthy subjects and CDAD and SAE patients under fasted state.

	Healthy subject <sup>120</sup>	CDAD and SAE Patients <sup>121</sup>
Stomach pH	1.0-2.5 <sup>122</sup>	4-7
Stomach fluid volume	45 ± 18 ml <sup>123</sup>	20-30 ml
Stomach transit time	0.25 hr <sup>124</sup>	Unknown but variable
Small intestine pH	4-7.4	pH 5 to >7
Small intestine fluid volume	Average 130 ml, range 10-150 ml	Low fluid volume
Small intestine transit time	3-4 hr	Unknown but variable
Large intestine pH	6-7	Unknown
Large intestine fluid volume	Average 10 ml, range as large as 125 ml	Unknown
Large intestine transit time	18 hr	Rapid transit with diarrhea
Colon	Smooth	Thickened dilated colon and pseudo membrane

Table 2. Vancomycin HCl solubility at different pH<sup>125</sup>

Vancomycin HCl solubility and volume required to dissolve Vancomycin HCl in 250 mg Vancomycin HCl capsules, Data as mean±S.D., N=3 samples/test					
pH	1.0	3.0	4.0	5.0	7.5
Solubility (mg/ml)	140.3±0.7	191.7±0.2	2.98±0.03	9.5±0.2	17.5±0.2
Volume (ml)	1.8	1.3	83.9	26.3	14.3

<sup>119</sup> Willmann S., et al., A Physiological Model for the Estimation of the Fraction Dose Absorbed in Humans, at 4.

<sup>120</sup> Sutton, S.C., "Role of Physiological Intestinal Water in Oral Absorption," *The AAPS J.* 2009, 11:277-285.

<sup>121</sup> Unless noted otherwise, the information in this table related to CDAD and SAE patients was provided by ViroPharma. See

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/UCM179424.pdf>.

<sup>122</sup> Evans, D.F., Pye, G., Bramley, R., Clark, A.G., et al. "Measurement of Gastrointestinal pH Profiles in Ambulant Human Subjects." *Gut*, 1988, 29: 1035-1041.

<sup>123</sup> Schiller, C., Fröhlich, C.P., Giessmann, T., Siegmund, W., et al., "Intestinal Fluid Volumes and Transit of Dosage Forms as Assessed by Magnetic Resonance Imaging." *Aliment Pharmacol Ther.* 2005, 22(10):971-9.

<sup>124</sup> Ramsbottom, N., Knox, M.T., Hunt, J.N.. "Gastric Emptying of Barium Sulphate Suspension Compared With That of Water." *Gut*, 1977, 18:541-542.

<sup>125</sup> The data in this table are from the 2008 DPQR study determining the solubility of Vancocin oral capsules. DPQR 2008 Solubility Study at 17.

(b) Section 505(j) of the FD&C Act Does not Require an ANDA Applicant to Separately Demonstrate Safety and Effectiveness of Generic Products in Patient Populations

You generally maintain that various characteristics of the GI tract of the patient subpopulation can affect dissolution and performance of the vancomycin capsule, and that dissolution methodologies that do not reflect the in vivo environment of CDAD patients are inadequate to demonstrate bioequivalence. You mischaracterize the nature of the bioequivalence evaluation.

As described in section I.B, above, an ANDA applicant is not required to demonstrate through clinical endpoint trials that its product is safe and effective for the labeled conditions of use. Rather, it can rely on the finding of safety and effectiveness of the RLD as long as the product meets other requirements of the statute, including demonstrating that the proposed generic product is bioequivalent to the RLD. The purpose of bioequivalence testing is to evaluate whether the particular formulation described in the ANDA delivers the active ingredient to the site of action at the same rate and to the same extent as the RLD.

Vancocin is a simple capsule containing vancomycin and one inactive ingredient (polyethylene glycol 6000). As described in the Draft Vancomycin BE Guidance, the solubility and relatively fast dissolution rate of vancomycin ensures that the product forms a solution and stays a solution before it reaches the site of action in the GI tract.<sup>126</sup> If the proposed product is Q1/Q2 the same with respect to active and inactive ingredients to the RLD, then, as discussed below, the only difference that would affect the bioavailability at the site of action in the GI tract is a variation in the rates of dissolution of the two products, a property that can be measured accurately in vitro for highly soluble drugs.<sup>127</sup> Contrary to your underlying premise, an ANDA applicant for generic vancomycin does not have to submit data from tests that use all potential in vivo conditions of CDAD and SAE patients. Instead, data from a given range of conditions, discussed in detail below, are sufficient to demonstrate that the proposed product will perform the same as the RLD in all relevant conditions.

Although you cite various factors that may affect in vivo dissolution of vancomycin capsules, you have not provided any evidence to show that these patient-related factors, if evaluated in vivo in CDAD patients, would identify *differences in formulation* that might have clinical significance and that would not be identified by FDA's recommended in vitro dissolution testing. To the extent that the bioavailability of Vancocin could be affected by these factors, if at all, these factors can be expected to affect the bioavailability of a Q1/Q2 generic vancomycin product for which bioequivalence to

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<sup>126</sup> Draft Vancomycin BE Guidance, at 2-3. See DPQR 2008 Dissolution Study at 34 (vancomycin products dissolve faster than 85% in 45 minutes); DPQR 2008 Solubility Study at 17 (concluding vancomycin products are highly soluble under BCS Guidance standards).

<sup>127</sup> Galia, E.; Nicolaides, E.; Hörter, D.; Löbenberg, R.; Reppas, C. and Dressman, J.B., "Evaluation of Various Dissolution Media for Predicting In Vivo Performance of Class I and II Drugs," *Pharm Res* 1998, 15(5), 698-705.

Vancocin is established through in vitro dissolution data to the same extent they would be expected to affect the bioavailability of Vancocin. FDA addresses the individual patient-related factors you cite in detail below.

(c) In Vitro Dissolution Media

You assert that FDA has not adequately accounted for the unique nature of fluid in the GI tracts of CDAD patients. Specifically, you assert that “the contents of the GI tract in patients with CDAD are highly abnormal and differ significantly from the simple, buffered solution suggested for use by OGD.”<sup>128</sup> You claim that the GI contents of CDAD patients “include many components such as exudates, proteins, inflammatory mediators, cellular debris, blood and other biologic components that are very difficult if not impossible to simulate in an in vitro medium.”<sup>129</sup> You suggest that the influence “of any of these factors on the availability at the site of action will not be predicted by the proposed in vitro testing.”<sup>130</sup> You also note that other commentators to the Draft Vancomycin BE Guidance proposed use of Simulated Gastric Fluid and Simulated Intestinal Fluid in addition to the media proposed in the draft guidance.<sup>131</sup>

However, to design an appropriate in vitro dissolution study, the main objective is to select an in vitro condition which has a balance between adequately reflecting in vivo conditions in which vancomycin capsules are dissolved, and a condition that is sufficient for evaluation of the product formulation. The main factors in the selection of the dissolution media are the pH (addressed later), volume, and the potential addition of surfactants to help solubilize the drug after it leaves the formulation. Because of vancomycin’s high solubility, the addition of surfactants like those found in simulated intestinal fluid is not recommended when conducting in vitro dissolution testing because they can hasten solubilizing and therefore affect the ability to identify differences in dissolution rate between vancomycin products. Dissolution testing using an aqueous solution without surfactants is as good as or better to evaluate the formulation performance for highly soluble drug products than are simulated gastric or intestinal fluid.<sup>132</sup>

(d) Lower and Upper pH Levels

You claim that the pH levels FDA recommends for the in vitro bioequivalence dissolution testing for vancomycin capsules do not adequately account for the physiology

<sup>128</sup> VP June 30, 2006, Supp. at 26-27.

<sup>129</sup> Id. at 26.

<sup>130</sup> Id. at 26-27.

<sup>131</sup> VP Draft Guidance Resp. at 11.

<sup>132</sup> Hörter, D. and Dressman, J.B. “Influence of Physicochemical Properties on Dissolution of Drugs in the Gastrointestinal Tract,” 2001, *Adv Drug Delivery Rev* 46(1-3), 75-87; Nicolaides, E.; Galia, E.; Efthymiopoulos, C.; Dressman, J.B., and Reppas, C., “Forecasting the In Vivo Performance of Four Low Solubility Drugs From Their In Vitro Dissolution Data,” 1999, *Pharm Res* 16 (12), 1876--82; Galia, E.; Nicolaides, E.; Hörter, D.; Löbenberg, R.; Reppas, C., and Dressman, J.B. “Evaluation of Various Dissolution Media for Predicting In Vivo Performance of Class I and II Drugs,” 1998, *Pharm Res* 15(5), 698--705.

and pH of the GI tract of patients most susceptible to CDAD, including elderly patients.<sup>133</sup> You also contend that the relevance of dissolution at the lower pH levels of 1.2 and 4.5 “is questionable,” that a pH level of 6.8 does not account for potential levels at 7.0 and higher,<sup>134</sup> and, more generally, that variability associated with dissolution testing complicates its use in bioequivalence assessment.<sup>135</sup> You claim that FDA disregarded scientific articles that observed the importance of accurate pH levels in dissolution testing for specific populations.<sup>136</sup> Finally, you contend that the pH range is inconsistent with the range used by FDA in its 2008 internal study of vancomycin solubility.<sup>137</sup>

The dissolution characteristics of oral formulations are often evaluated in the physiologic pH range of 1.2 to 6.8, and FDA consistently recommends this pH range for dissolution testing.<sup>138</sup> The three dissolution media (pH 1.2, 4.5, and 6.8) in the recommended vancomycin dissolution study reflect a range of pH conditions that will ensure that test and reference products will release drug similarly over the range of in vivo environments that may be encountered in the patient population. FDA has determined that these three testing points cover a sufficient range to allow the conclusion that relative dissolution of test and reference products would be similar at any other pH conditions in the relevant portions of the GI tract.

With respect to the upper pH limit in particular, FDA has determined that 6.8 is the appropriate upper pH level for the vancomycin dissolution testing. As indicated above, it is commonly used as an upper pH condition for dissolution testing of IR products. It represents a higher pH than is often present in the small intestine. In addition, as indicated in the vancomycin solubility profile (Table 2), vancomycin has a higher solubility at pH 7.5 than 6.8. For the same formulation, the dissolution rate would increase with an increase in drug solubility due to pH changes; thus, if the test formulation dissolves more slowly than the RLD, a dissolution test at pH 6.8 will be more sensitive than pH 7.5 to detect the dissolution difference.<sup>139</sup>

<sup>133</sup> VP June 30, 2006, Supp. at 28-29.

<sup>134</sup> Id. at 28-29.

<sup>135</sup> Id. at 32-33 (citing concerns with dissolution testing that may result from multiple calibration points, undefined parameters and differences in excipients).

<sup>136</sup> VP Draft Guidance Resp. at 14-15.

<sup>137</sup> Id. at 11-12.

<sup>138</sup> See BCS Guidance, at 2 (Aug. 2000); guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, at 6 (Aug. 1997).

<sup>139</sup> Guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, at 6 (Aug. 1997) (recommending upper pH level of 6.8 as sufficient). You point to the fact that FDA used an upper pH level of 7.5 in its DPQR 2008 Dissolution Study in support of your argument that FDA should require dissolution data up to the pH level of 7.5. Your reference to the highest level pH of 7.5 used in the DPQR 2008 Solubility Study is misplaced. FDA used the upper pH level of 7.5 in the solubility study, and determined that vancomycin has a higher solubility at pH 7.5 than 6.8. Accordingly, FDA concluded that the upper pH for dissolution assessment should be 6.8, because use of pH higher than that would be less sensitive due to the increased solubility.

In addition, these and the other precise specifications for dissolution comparison set out in the Draft Vancomycin BE Guidance and discussed in this petition response, including the Q1/Q2 requirement, adequately address your concerns regarding variability that may be associated with dissolution testing.

(e) Dissolution Media Volume

You next argue that fluid volume in the upper GI tract of CDAD patients is likely to be substantially lower than the 500 ml-1000 ml volumes cited by FDA in the Draft Vancomycin BE Guidance in support of the Agency's recommendation of a volume of 900 ml for the in vitro dissolution analysis.<sup>140</sup> You further assert that the authors of the scientific article FDA cites in support of its recommended fluid volume do not support FDA's dissolution methodology, because those authors proposed the values based on reports from healthy patients for a different purpose than comparative in vitro dissolution for vancomycin products. In addition, you claim that it cannot be assumed that the volume of fluid in an upper GI tract of a CDAD patient is likely to be the same as a healthy non-fasted individual, and is likely to be less.

Your arguments are misplaced. Normally, for the basket and paddle apparatus that FDA recommends in the Draft Vancomycin BE Guidance, the volume of the dissolution medium is 500 mL to 1000 mL, with 900 mL as the most common volume.<sup>141</sup> FDA recommends 900 ml for the vancomycin dissolution study because it provides sufficient fluid volume to completely dissolve all vancomycin doses.

Based on the fluid volumes generally present in the GI tract, most vancomycin dissolution takes place in an in vivo environment where the entire dose can be dissolved. As shown in Table 2, the dissolution media volume at pH 1.2 and 6.8 to reach complete dissolution for a 250 mg vancomycin dose is less than 50 ml. At pH 4.0, vancomycin has the lowest solubility and the dissolution media volume to ensure "sink condition" (the volume of medium at least greater than three times that required to form a saturated solution of a drug substance) for full dissolution of 250 mg vancomycin dose is about 255 ml. Therefore, based on vancomycin solubility, the proposed 900 ml dissolution medium provides test conditions where the vancomycin capsule can completely dissolve.

Even if in particular individuals there is potentially insufficient physiological fluid volume for complete release of vancomycin HCl from formulations, FDA has determined that equivalent dissolution profiles at different pH conditions that would be encountered in the GI tract ( $f_2 > 50$ ) will ensure that equivalent amounts of vancomycin from the generic and RLD formulations are available. Accordingly, assuming that the test product formulations are Q1 and Q2 the same as the RLD in a capsule, it is FDA's determination that Vancocin and a proposed vancomycin generic product will not behave differently in vivo provided they have comparable in vitro dissolution at the different pH conditions specified above.

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<sup>140</sup> VP Draft Guidance Resp. at 12-13; VP June 30, 2006, Supp. at 38.

<sup>141</sup> USP General Chapter on Dissolution <711> (USP 34-NF 29) (official through April 30, 2012).

In addition, if an individual has a low fluid volume in the GI tract, no vancomycin formulation can provide a higher concentration than the vancomycin solubility (the maximum amount of vancomycin that will dissolve in a specific amount of liquid) permits. Even at vancomycin's lowest solubility of  $2.98 \pm 0.03$  mg/ml at pH 4.0 (see Table 2 above), the concentration of vancomycin is over 180-fold higher than the 0.016 mg/mL minimum inhibitory concentration (MIC) (the minimum antibiotic concentration needed to inhibit bacterial growth) estimated in the literature.<sup>142</sup> In other words, even if some portion of Vancocin or a generic vancomycin product does not dissolve due to insufficient liquid, no significant safety and efficacy difference will be expected because there will be adequate concentration to kill the bacteria which causes CDAD.

(f) Solubility

You claim that while vancomycin is highly soluble at low pH levels, solubility is pH dependent, and that FDA's reliance on the highly soluble characteristic of vancomycin in healthy subjects is not relevant in the context of CDAD patients.<sup>143</sup> Specifically, you assert that the administration of vancomycin capsules to CDAD patients who have low gastric fluid volume "may greatly exceed the solubility of vancomycin, particularly in the presence of elevated intragastric pH observed in such patients."<sup>144</sup> In other words, you argue that the gastric fluid volume in certain CDAD patients is too low to completely solubilize the vancomycin dose and therefore that the vancomycin in a capsule will not be fully released.

Your assertions with respect to solubility are based on your concern about the fluid volume in the patient population. The previous section discusses this issue, and for the reasons set forth there, your assertions regarding solubility lack merit.

(g) Transit Times

You also challenge FDA's statement in the Draft Vancomycin BE Guidance that "vancomycin HCl is highly soluble at pH conditions encountered in the GI tract and expected to be in solution long before it reaches the site of action in the lower GI tract."<sup>145</sup> You assert that the recommended dissolution method does not accurately account for potentially reduced transit times as short as 1-2 hours.<sup>146</sup> Your argument with respect to transit times is misplaced because, as previously stated, FDA's bioequivalence recommendation centers on the similarity of dissolution profiles between test and reference products. Test and reference products with similar dissolution profiles in the recommended tests will provide similar drug release in patients with much shorter GI

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<sup>142</sup> Dzink, J., Bartlett, J.G. "In Vitro Susceptibility of *Clostridium difficile* Isolates From Patients With Antibiotic-Associated Diarrhea or Colitis." 1980, *Antimicrob Agents Chemother* 17:695-8

<sup>143</sup> VP June 30, 2006, Supp. at 38.

<sup>144</sup> Id. at 38-39.

<sup>145</sup> Draft Vancomycin BE Guidance at 3.

<sup>146</sup> VP Draft Guidance Resp. at 15-17.

transit times. In addition, even the 1-2 hours transit time you mentioned is sufficient to provide complete release of vancomycin.<sup>147</sup>

(h) Potential Systemic Absorption

You assert that FDA has not sufficiently taken into account the potential systemic absorption of vancomycin in CDAD patients as indicated in the Vancocin labeling.<sup>148</sup> The Vancocin Capsule label states: “[v]ancomycin is poorly absorbed after oral administration.”<sup>149</sup> This is the primary reason that the in vivo bioavailability study was waived during the NDA approval.<sup>150</sup> Vancomycin permeability is very low and vancomycin is poorly absorbed in patients. Therefore, recommending in vivo pharmacokinetic studies comparing generic and RLD products offers little benefit, as neither product would be expected to produce detectable plasma vancomycin concentrations. Even if the rare subset of patients with increased permeability could be identified for study and the in vivo plasma vancomycin concentrations in these patients could be measured and quantified,<sup>151</sup> generic and RLD vancomycin HCl capsules with the same excipients and similar dissolution profiles would be expected to have the same plasma concentration profiles in these patients.

(i) Site of Action in SAE Patients

You contend that FDA did not adequately take into account the site of action in SAE patients in the upper GI tract and small intestine because FDA’s position that there is sufficient upper GI transit time for a vancomycin capsule to fully solubilize before it reaches the site of action in the lower GI tract, does not address the SAE site of action in the upper GI tract.<sup>152</sup> Again, you misconstrue the bioequivalence analysis. In those SAE patients who may have infection in the upper GI tract, equivalent in vitro dissolution profiles at multiple pH conditions will ensure equivalent amounts of vancomycin are delivered to each site by both generic and RLD formulations, even in the upper GI tract.

(j) Predictability of In Vivo Performance

You maintain that there are cases where in vitro dissolution has not been predictive of in vivo performance.<sup>153</sup> The three drugs mentioned are mesalamine, mebendazole, and propantheline bromide. Without addressing the merits of ViroPharma’s claim that these are instances in which in vitro dissolution was not predictive of in vivo performance,

<sup>147</sup> DPQR 2008 Dissolution Study at 34 (vancomycin products dissolve faster than 85% in 45 minutes). For this reason, ViroPharma’s reference to the finding of Navaneethan and Giannella that CDAD has been observed in the small bowel in some patients (assuming this finding to be true), does not change our conclusions. VP May 18, 2009, Supp. at 1-2.

<sup>148</sup> VP June 30, 2006, Supp. at 17-20; VP Draft Guidance Resp. at 25-26.

<sup>149</sup> Vancocin PI, at 9.

<sup>150</sup> Biopharmaceutical Recommendation for Approval of Vancomycin Hcl 125 and 250 mg Capsules, Summary Basis of Approval for NDA 50606, at 40 (May 30, 1985).

<sup>151</sup> See Vancocin PI at 3.

<sup>152</sup> VP Draft Guidance Resp. at 28-29.

<sup>153</sup> VP June 30, 2006 Supp. at 33.

FDA notes that these three drugs all have significant differences from vancomycin that indicate the inappropriateness of this comparison. Vancomycin is a high solubility drug at all pH levels and Vancocin Capsules are an immediate release dosage form. The mesalamine products mentioned are modified release products, which means that they are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time rather than immediately. In addition, mesalamine solubility varies from high to low depending on pH.<sup>154</sup> With respect to mebendazole, it is a low solubility drug.<sup>155</sup> Finally, the published reports of propantheline bromide dissolution problems have been linked to excipient effects.<sup>156</sup> None of these examples is relevant to the dissolution of high solubility drugs using the same excipients, as is recommended in the Draft Vancomycin BE Guidance, because they differ in characteristics (solubility, release function, and inactive ingredients) that, as discussed in this response, form the core of FDA's consideration of the scientific appropriateness of using dissolution data to demonstrate bioequivalence.

### 3. Q1/Q2 Sameness Requirement for Using In Vitro Dissolution Method to Demonstrate Bioequivalence

#### (a) Q1 Sameness: Polyethylene Glycol 6000 NF Satisfies the Q1 Sameness Requirement for Generic Vancomycin Capsules

Vancocin labeling states that "[t]he [Capsules] contain vancomycin hydrochloride equivalent to 125 mg (0.08 mmol) or 250 mg (0.17 mmol) vancomycin. The [Capsules] also contain F-D & C Blue No. 2, gelatin, iron oxide, polyethylene glycol [PEG], titanium dioxide, and other inactive ingredients."<sup>157</sup> The technical grade of PEG used in Vancocin Capsule is PEG 6000.<sup>158</sup>

As a preliminary matter, FDA concludes that generic products should use a PEG with the same technical grade of 6000 as Vancocin to demonstrate Q1 sameness. Many inactive ingredients are available in different technical grades. Technical grades frequently are differentiated by physical characteristics (e.g., the particle size, morphology differences in different grades of lactose and microcrystalline cellulose) or chemical structures (molecular weight difference of polysorbate esters and polyethylene glycols).<sup>159</sup> Technical grades may also differ in impurities and impurity profiles. Usually excipients

<sup>154</sup> Fadda, H. M.; Sousa, T.; Carlsson, A. S.; Abrahamsson, B; Williams, J. G; Kumar, D.; and Basit Mol, A. W., "Pharmaceutics, Drug Solubility in Luminal Fluids from Different Regions of the Small and Large Intestine of Humans," at 1527-32, *Molecular Pharmaceutics*, 2010: 7(5).

<sup>155</sup> Swanepoel E.; Liebenberg, W.; de Villiers, M.M., "Quality Evaluation of Generic Drugs by Dissolution Test: Changing the USP Dissolution Medium to Distinguish Between Active and Nonactive Mebendazole Polymorphs," at 345-349, *Eur. J. Pharm Biopharm.* 2003 May; 55(3).

<sup>156</sup> Abd El-Fattah, Sawzan; Khalil, Saleh A.H., "Variations in Dissolution Rates of Sugar-Coated Chlorpromazine Tablets," at 225-234, *International Journal of Pharmaceutics*, 1984: 18(3).

<sup>157</sup> Vancocin PI, at 8.

<sup>158</sup> ViroPharma, Presentation, at 30, Aug. 4, 2009 ACPS Meeting, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/UCM179424.pdf>.

<sup>159</sup> Moreton, R.C. "Excipient Functionality." May 2004 *Pharma Tech*.  
<http://pharmtech.findpharma.com/pharmtech/data/articlestandard//pharmtech/192004/94554/article.pdf>.

with different technical grades have different specifications and/or functionality, and performance.<sup>160</sup> According to FDA's guidance for industry on *Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (SUPAC IR Guidance), a change in the technical grade of an excipient is considered a Level 2 change, and requires the submission of a Prior Approval Supplement, including chemistry and dissolution documentation.<sup>161</sup>

As a general matter, if there are multiple grades of an inactive ingredient available and the NDA applicant specifies the technical grade of the excipient in the RLD labeling, generic products claiming to be Q1/Q2 to the corresponding RLD should contain the same technical grade of inactive ingredients used in the RLD, unless the ANDA applicant demonstrates that the difference in excipient technical grade does not affect drug product quality, manufacturability, performance, safety, and efficacy.<sup>162</sup> In the majority of cases, if the inactive ingredient is the subject of a United States Pharmacopeia (USP)/National Formulary (USP/NF) monograph, inactive ingredients used in RLD and generic products comply with that monograph's provisions.

FDA has concluded that for the purposes of vancomycin capsules, PEGs with different molecular weight differ significantly in terms of physicochemical and toxicological properties.<sup>163</sup> Therefore, we would expect an ANDA applicant for generic vancomycin capsules to use PEG with a molecular weight of 6000 in order to demonstrate Q1

<sup>160</sup> SUPAC-IR Questions and Answers about SUPAC-IR Guidance (1997).

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124826.htm>.

<sup>161</sup> Guidance for industry on *Immediate Release Solid Oral Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (Nov. 1995), at 8 (Level 2 change defined as "those that could have a significant impact on formulation quality and performance").

<sup>162</sup> As provided in the Draft Vancomycin BE Guidance, if a product is not Q1/Q2 to vancomycin, it may use in vitro dissolution to demonstrate bioequivalence if "the ANDA sponsor provides evidence that the differences in excipients will not affect the safety or efficacy of the proposed generic drug product." Draft Vancomycin BE Guidance at 3. FDA notes that several comments to the Draft Vancomycin BE Guidance docket maintained that in certain instances FDA should retain some flexibility in requiring Q1/Q2 sameness. See, e.g., Wockhardt Ltd. Submission, at 1 (Feb. 6, 2010) (Docket No. 2008-626) (maintaining that dissolution data should be permissible to demonstrate bioequivalence notwithstanding "minor qualitative and quantitative changes in the test formulations which are not intended to affect the transport of [v]ancomycin through the GIT and/or effectiveness of the drug at the site"); Encap Drug Delivery Submission, at 1-2 (Feb. 5, 2009) (Docket No. 2008-626) ("it is recommended that the Q2 criteria be removed or be qualified to 'quantitatively similar'"). FDA will consider on a case-by-case basis any applications for products that deviate from the Q1/Q2 requirement that seek to rely on in vitro dissolution data to demonstrate bioequivalence.

<sup>163</sup> See, generally, Biondi, O., Motta, S., Mosessa. "Low Molecular Weight Polyethylene Glycol Induces Chromosome Aberrations in Chinese Hamster Cells Cultured In Vitro." 2002, *Mutagenesis*. 17: 261-264. PEGs with a molecular weight below ~600 are clear, viscous liquids, while at a molecular weight of ~1000 PEGs appear as white waxy solids. In general PEGs are water soluble, stable, nontoxic compounds that do not hydrolyse or deteriorate on storage. When administered orally the higher molecular weight PEGs appear to be less toxic than low molecular weight polymers because the latter are absorbed by the digestive tract, whereas larger polymers are absorbed more slowly or not at all.

sameness.<sup>164</sup> Use of PEG 6000 will ensure that any material differences that may exist between PEGs that might affect the performance of a proposed generic vancomycin capsule are not present.

Next, you assert that Vancocin contains a trade secret inactive ingredient whose identity and quantity are not publicly known. You assert that this ingredient potentially has a link to antibiotic potency, and therefore that only generic vancomycin capsules that include that inactive ingredient may be approved.<sup>165</sup> We do not agree. Vancocin has one inactive ingredient inside the shell capsule: polyethylene glycol 6000, and you have not demonstrated that the PEG 6000 used in Vancocin, or any components therein, have a unique link to antibiotic potency such that generic vancomycin products must use the specific PEG found in Vancocin in order to be Q1.<sup>166</sup> Rather, FDA has concluded that generic vancomycin capsule products that comply with the USP/NF monograph for PEG satisfy the Q1 requirement, provided that the generic vancomycin products demonstrate the other requirements for Q1 sameness discussed here and have acceptable drug product stability and other quality attributes.

(b) Q2 Sameness: The Concentration of Inactive Ingredients Should Not Differ More Than 5% From the RLD.

We conclude that in order to demonstrate Q2 sameness, the concentration or amount of PEG 6000 in generic vancomycin should not differ by more than 5% of the concentration or amount in Vancocin. “Quantitatively the same” has been determined by CDER, in the context of locally acting drugs, to mean that the concentration or amount of the inactive ingredient(s) in the test product would not differ by more than “5 percent of the concentration or amount in the reference listed drug.”<sup>167</sup>

<sup>164</sup> We note that sameness in technical grade is not always required to demonstrate same formulation. See the draft guidance for industry on *Submission of Summary Bioequivalence Data for ANDAs*, at 4 (April 2009) available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM134846.pdf>.

<sup>165</sup> VP Draft Guidance Resp., at 44-46; VP Oct. 6, 2009, Supp. at 5-6; VP Dec. 18, 2009, Supp. at 1-3; VP July 25, 2010, Supp. at 12-14.

<sup>166</sup> FDA has fully considered your arguments related to this issue, but has refrained from including the full discussion here in order to preserve any of your confidential commercial or trade secret information contained therein.

<sup>167</sup> Draft guidance for industry on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*, at 8 (April 2003); FDA Citizen Petition Response re: Derma-Smoother/FS (fluocinolone acetonide 0.01% Topical Oil (Docket No. 2004-P-0215) at 13-14 (Mar. 25, 2009) (locally acting topical oil considered Q2 if quantity of each inactive ingredient no more than 5% different than RLD)). See also SUPAC IR Guidance at 7 (no new bioequivalence data required for changes in total additive effect of all excipient changes of 5% or less).

4. Q3 Sameness Is Unnecessary to Demonstrate Vancomycin Bioequivalence When Using In Vitro Dissolution Data

You propose that FDA should consider requiring “Q3” sameness for generic vancomycin.<sup>168</sup> Upon consideration of your arguments and the relevant scientific materials, FDA concludes that Q3 sameness is not required for demonstrating bioequivalence of vancomycin capsules.

Q3 sameness is a relatively new concept in bioequivalence evaluations, and generally means the formulations have the same structural characteristics in terms of components, concentration, and microstructure.<sup>169</sup> In the August 4, 2009, ACPS Meeting that concerned the Draft Vancomycin BE Guidance, Dr. Patrick K. Noonan from Virginia Commonwealth University suggested the following factors for Q3 sameness for vancomycin capsules:

- Individual ingredient quality attributes
  - Testing beyond pharmacopeial requirements
  - Particle size
  - PEG molecular weight distribution
  - Polymorphic control
- Manufacturing process variables
  - Temperature, humidity, pressure
  - API milling speed
- PEG melt characteristics
  - Hot melt viscosity<sup>170</sup>

FDA declines to adopt Dr. Noonan’s Q3 criteria for vancomycin, or otherwise to require ANDA applicants to demonstrate Q3 sameness.

For complex formulations other than solutions, such as topical creams, gels, and ointments, it is possible that Q1/Q2 formulations may result in different drug product properties based on different manufacturing process (e.g., a drug product manufactured by simply blending all components may have different dissolution and stability characteristics from the one manufactured by a hot melt process). However, vancomycin capsule is a simple solid oral dosage form and it need not maintain its microstructure to exert its pharmacological action because it goes through a dissolution process in vivo before it reaches the site of action. FDA reviewers routinely examine dissolution and stability characteristics, and ensure that any difference in manufacturing process from the RLD will not affect finished drug product quality and performance.

<sup>168</sup> VP Draft Guidance Resp. at 42-43.

<sup>169</sup> Wilkin, J., Presentation: The Pursuit of Alternative Methodologies For Demonstrating Bioequivalence for Generic Topical Dermatologic Drug Products: DPK, Q3, Cakes, and 2 PIs, Presentation, ACPS Meeting (Oct. 22, 2003).

<sup>170</sup> 2009 ACPS Tr., at 144-148.

In addition, under “Quality by Design” (QbD) principles, ANDA applicants are encouraged to identify and monitor critical attributes of excipients, drug substance, in-process material, and finished products, as well as critical process parameters. Within FDA’s current “Question-based review” (QbR) system, ANDA reviewers will evaluate these critical attributes and critical process parameters to ensure approval of quality generic products.

5. FDA’s DPQR Vancomycin 2008 Dissolution Study Was Not Faulty

As described above, OGD commissioned a study in 2006 with CDER’s DPQR to determine the dissolution characteristics of Vancocin Capsules.<sup>171</sup> DPQR completed the study in February 2008, and concluded that vancomycin drug products were found to dissolve faster than 85% in 45 minutes at a range of predetermined pH conditions encountered in the GI tract, with the exception of two lots of the RLD drug.<sup>172</sup> The study observed that vancomycin capsules are not “rapidly” dissolving as defined in the “BCS Guidance,” however, which requires 85% dissolution within 30 minutes at the predetermined pH levels.<sup>173</sup> DPQR repeated the study in 2009 and confirmed the 2008 results.<sup>174</sup>

You assert that the DPQR Vancomycin 2008 Dissolution Study was faulty on several grounds: (1) FDA used expired vancomycin capsules; (2) FDA used test products that had “meaningfully high overages;” and (3) FDA improperly used a noncompendial method for assessing dissolution characteristics of oral vancomycin.<sup>175</sup>

Upon review of the study, FDA finds your concerns regarding the 2008 dissolution study unsupported. First, the dissolution experiments described in the 2008 report were conducted in 2006, when the lots used to assess Vancocin dissolution had not yet expired. Second, as you note, samples of vancomycin products other than Vancocin also were evaluated in the 2008 study. Although FDA assessed the dissolution of these products, the Agency did not use data from any non-Vancocin product in determining that Vancocin dissolved more than 85% in 45 minutes. Similarly, although certain proposed vancomycin products demonstrated vancomycin release in the 109-116% range, these products were not used in determining the dissolution of vancomycin in Vancocin. Your concerns regarding FDA’s use of a noncompendial method for assessing dissolution characteristics of oral vancomycin are addressed below.

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<sup>171</sup> DPQR 2008 Dissolution Study.

<sup>172</sup> Id. at 34.

<sup>173</sup> Id. at 14.

<sup>174</sup> DPQR 2009 Dissolution Study (July 30, 2009).

<sup>175</sup> VP Draft Guidance Resp., Appendix A at 63-64.

6. Use of the High Performance Liquid Chromatographic Assay Method for Vancomycin Capsules Is Appropriate to Determine In Vitro Dissolution Profiles

FDA does not indicate in the Draft Vancomycin BE Guidance a specific analytical procedure for generating dissolution profiles. Rather, for products that are the subject of product-specific guidances, the Agency generally recommends the approaches laid out in FDA's guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.<sup>176</sup> Those approaches depend on the existence of the USP official compendial test and the nature of the dissolution test employed for the RLD.<sup>177</sup> To determine the appropriate methodology to assess dissolution of vancomycin capsules, FDA took several steps, including: (1) review of the USP monograph requirements on vancomycin HCl and vancomycin HCl capsules; (2) evaluation of the practices that ViroPharma, the RLD holder; and (3) analysis of the suitability of using a high performance liquid chromatographic (HPLC) method to assess comparative dissolution of vancomycin HCl capsule formulations. As part of this evaluation, FDA also considered whether USP vancomycin reference standards and/or other qualified vancomycin reference standards can be used in HPLC analysis of comparative dissolution of vancomycin HCl capsule formulations. From this analysis, FDA concludes that use of an HPLC method to assess comparative dissolution of vancomycin capsules is appropriate, and that USP vancomycin reference standards and/or other qualified vancomycin reference standards can be used in HPLC analyses.

You assert that FDA should not permit ANDA applicants to use an HPLC method to assess comparative dissolution of vancomycin HCl capsule formulations.<sup>178</sup> FDA disagrees. Your specific arguments on this issue are addressed in detail below.

(a) Existing USP Monograph Requirements on Vancomycin HCl Active Pharmaceutical Ingredient (API) and Vancomycin HCl Capsules

The USP vancomycin HCl drug substance monograph directs that the assay performed to assess compliance with USP standards of strength should be the USP microbial assay, with specification of not less than (NLT) 900 µg of vancomycin per mg on the anhydrous basis against a USP Vancomycin Hydrochloride reference standard (RS).<sup>179</sup> Vancomycin is a mixture of similarly structured compounds, with vancomycin B being the compound of greatest abundance.<sup>180</sup> The vancomycin components vary in microbiological activity; therefore, the microbiological assay yields a result representing a concentration-weighted summation of the individual components' activities.

<sup>176</sup> Guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* (Aug. 1997) at 5.

<sup>177</sup> *Id.*

<sup>178</sup> VP June 25, 2010, Supp.; VP July 20, 2010, Supp..

<sup>179</sup> USP Monograph on Vancomycin Hydrochloride, USP 32 - NF 29 through Second Supplement (remains official until April 30, 2012), at 4565-66.

<sup>180</sup> Best, G.K. Best, N.H., and Durham, N.N. "Chromatographic Separation of the Vancomycin Complex." 1968, *Antimicrob. Agents Chemother.*, 4 115.

The USP vancomycin HCl drug substance monograph directs that the Chromatographic Purity test should be performed by an HPLC method with peak area percentage of NLT 85% of vancomycin B and no more than (NMT) 5% of any other peak.<sup>181</sup> USP Vancomycin Hydrochloride RS is used to prepare the resolution solution, but is not used for calculation of the purity. This HPLC test was adopted for vancomycin in USP 23 in 1995.<sup>182</sup> Due to the complexity of the vancomycin chromatograms, the fundamental assumption for the evaluation of vancomycin HCl is that the molar absorptivities of the vancomycin-related compounds in the drug substance are approximately equal. This assumption was confirmed by several spectroscopic and chromatographic experiments.<sup>183</sup> The basic assumption of similar molar absorptivities permits measurement of vancomycin B and other related components. Wavelength selection is not critical, because most vancomycin related substances have similar UV absorption spectra, with the optimum wavelength determined by sensitivity requirements.

USP directs that the Limit of Monodechlorovancomycin (MDCV) test also should be performed by HPLC method with weight/weight (w/w) percentage NMT 4.7%. In the USP reference standard for this test, Vancomycin B with Monodechlorovancomycin RS, the purity of vancomycin B is expressed as mg per mg. This test was added in the Second Supplement to USP 30 in 2007.<sup>184</sup> The same assumption made in Chromatographic Purity is applied in the MDCV test as well: the molar absorptivity of MDCV is approximately equal to that of vancomycin B.

The USP drug product monograph directs that the quantitative analysis of vancomycin HCl oral capsule content should be performed using USP microbial assays.<sup>185</sup> USP also states that the microbial assay should be used in the quality control dissolution test. There is no assay provided in the USP vancomycin capsule monograph expressly directed toward comparative dissolution of vancomycin HCl capsules, so FDA must determine the most appropriate comparative assay.

FDA will require all ANDA applicants to apply USP monograph requirements for vancomycin hydrochloride and vancomycin hydrochloride capsules for stability and quality control of APIs and drug products.

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<sup>181</sup> HPLC uses different types of stationary phases, a pump that moves the mobile phase(s) and analyte through the column, and a detector to provide a characteristic retention time for the analyte. Analyte retention time varies depending on the strength of its interactions with the stationary phase, the ratio/composition of solvent(s) used, and the flow rate of the mobile phase. Rather than a summation of component activities like that generated by the microbiological assay, the HPLC method measures vancomycin B and other related components multiple times over the course of the execution of the assay. In other words, multiple, precise measurements of the presence of vancomycin B in two products over a set time period function as a surrogate for similar dissolution rate for those products.

<sup>182</sup> USP monograph of Vancomycin Hydrochloride, USP 23 - NF 18 (1995), page 1620.

<sup>183</sup> Inman, E.L. "Determination of Vancomycin Related Substances by Gradient High-Performance Liquid Chromatography. 1987, *J. Chromatography A*, 410 363-372.

<sup>184</sup> *Pharmacopeial Forum* 30(6), at 2055

(<http://www.usp.org/USPNF/revisions/usp30nf25secondSupplement05.html>).

<sup>185</sup> USP Monograph for Vancomycin Hydrochloride Capsules, USP 30 - NF 29 through second supplement (remains official until April 30, 2012), at 4566-67.

(b) Analytical Practices of RLD Holder for Analyzing Vancomycin HCl APIs and Vancocin Capsules

In light of your reference to ViroPharma's use of the microbial assay to assess batch variance,<sup>186</sup> FDA reviewed the Company's practices for analyzing Vancocin, and has concluded that nothing in ViroPharma's practices provides support for a determination that HPLC is not an appropriate method for assessing comparative dissolution. Due to the confidential nature of this information, the company's specific practices will not be discussed in this citizen petition response.

(c) Previous Comparative Dissolution Assessment of Vancomycin HCl Capsules by FDA

The Agency used an HPLC method to assess dissolution in the 2008 and 2009 DPQR Dissolution Studies.<sup>187</sup> As indicated in the 2008 study report, FDA's DPQR validated the HPLC analytical method used "according to USP category I for accuracy, precision, linearity, specificity and analytical range."<sup>188</sup> The study report also provided a detailed schedule of the validation parameters used.<sup>189</sup>

In your citizen petition filings, ViroPharma asserts that this validation was insufficient because FDA did not establish the relationship between biological assay testing and the HPLC assay. Without understanding this relationship, you claim, "it is possible that quantification of a single peak [via HPLC] is not an appropriate method of analysis or that only a set of specific and well-defined conditions for preparing and handling test and reference materials will provide reliable data."<sup>190</sup> This assertion is incorrect, because FDA does not seek to demonstrate something that would require cross-validation to the microbial methodology — for example, that the HPLC methodology demonstrates exactly what the microbial assay would demonstrate. Rather, the Agency seeks to establish the comparative dissolution rate of vancomycin using the most sensitive validated assay available, which, in the Agency's determination, is the HPLC method. While the Agency's guidance on dissolution testing for immediate release solid oral dosage forms instructs FDA to look to USP-recommended dissolution methodologies in certain circumstances,<sup>191</sup> the guidance does not recommend use of, or cross-validation to, a USP methodology in all circumstances in which dissolution is assessed.

<sup>186</sup> VP July 20, 2010, Supp. at 2-3.

<sup>187</sup> DPQR 2008 Dissolution Study at 9-10; DPQR 2009 Dissolution Study at 8. FDA notes that in the 2009 Vancomycin Dissolution study, the Agency used an ultra-performance liquid chromatographic (UPLC) method to evaluate dissolution rather than the HPLC method. DPQR 2009 Vancomycin Dissolution Study, at 8. As indicated in the DPQR 2009 Dissolution Study, FDA validated this methodology. Id. at 8-10. The UPLC method functions very similarly to the HPLC methodology, but as indicated in the study report, has certain benefits including speed of analysis. Id. at 8. While these benefits exist, they are not of such a nature that FDA would require ANDA applicants to use a UPLC method rather than the HPLC method. FDA will accept either method so long as it is adequately validated.

<sup>188</sup> DPQR 2008 Dissolution Study at 10. See also DPQR 2009 Dissolution Study at 8.

<sup>189</sup> DPQR 2008 Dissolution Study at 10. See also DPQR 2009 Dissolution Study at 8-9, 10.

<sup>190</sup> VP June 25, 2010, Supp. at 2.

<sup>191</sup> Guidance for industry on *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*, at 5.

You also assert that there were differences in the results between the 2008 and 2009 DPQR Dissolution Studies for Vancocin products from the same batch that demonstrate that the HPLC methodology has not been fully validated.<sup>192</sup> This is not the case. As indicated above, FDA fully validated the methods used in the 2008 and 2009 Dissolution Studies through accepted methods. There are multiple potential sources for differences in dissolution data of products from the same batch tested on two separate occasions, including product change over time, and capsule-to-capsule variations. None of these factors is relevant to whether the methods themselves were adequately validated.

(d) No Official USP Standard is Expressly Indicated for Assessing Comparative Dissolution

The Draft Vancomycin BE Guidance recommends “[d]issolution testing for stability and quality control: USP method.” As mentioned above, FDA will require all ANDA applicants to apply USP monograph requirements for vancomycin hydrochloride and vancomycin hydrochloride capsules for stability and quality control of APIs and drug products.

You argue that current generic applicants also must use the USP microbial method for assessing comparative dissolution of the test and reference products.<sup>193</sup> The microbial method is not an adequate replacement for the HPLC test. The USP microbial method is not expressly indicated for assessing comparative dissolution rates of two products, and the USP vancomycin capsule monograph does not otherwise include a comparative dissolution methodology. In other words, a methodology for measuring the comparative dissolution of two different vancomycin HCl capsule formulations is beyond the scope of the USP monograph. Use of the HPLC assay to measure comparative dissolution does not replace the USP microbial dissolution test, but rather is complementary to this quality control method, and is used to assess bioequivalence if the proposed generic formulations meet the Q1/Q2 criteria.

(e) Limitations of Microbial Assay, and the Growing Recognition of Superior Utility of HPLC Methodology for Measuring Comparative Dissolution

The USP microbial dissolution tests for vancomycin capsules were primarily adopted as a quality control tool to replace the use of disintegration tests, which had been official in the USP since 1950.<sup>194</sup> As you acknowledge, the USP vancomycin dissolution method with microbial assay is insufficient as the analytical technique for undertaking vancomycin bioequivalence analysis:

The USP vancomycin dissolution test was not developed for use as a bioequivalence method. Rather, its use has been in the release of batches of

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<sup>192</sup> VP July 20, 2010, Supp. at 7.

<sup>193</sup> VP July 20, 2010, Supp. at 3.

<sup>194</sup> Cohen, J.L., Hubert, B.B., Leeson, L.J., Rhodes, C.T., Robison, J.R., Roseman, T.J., Shefter, E. “The Development of USP Dissolution and Drug Release Standards. 1990, *Pharm Res.* 7 (10), 983-987.

vancomycin hydrochloride capsules. It does not measure the rate of dissolution of vancomycin capsules, but only whether a certain percent dissolution has occurred at a single time point. It is difficult to use, because of its narrow linear working range. It is not particularly precise. Its variability is sufficiently large to make interpretation of the f2 test problematic. In sum, the USP vancomycin dissolution test is unlikely to be capable of generating the type of dissolution profiles needed to permit the comparisons required in OGD's proposed vancomycin capsule BE method.<sup>195</sup>

By contrast, the USP monographs increasingly have recognized the general value of the HPLC methodology for various vancomycin analyses. Since the vancomycin monographs were first published, HPLC has become the official method for purity determinations for vancomycin HCl (added in 1995),<sup>196</sup> and for the test for Limit of monodechlorovancomycin (added in the 2<sup>nd</sup> supplement to USP 30 in 2007).<sup>197</sup> The HPLC method was adopted because of the recognition of its usefulness and effectiveness in a variety of settings, such as monitoring process changes, stability profiling, establishing improved accuracy in chemical purity determination, and tightening in-process controls.<sup>198</sup>

Such a trend of generally recognizing the superiority of HPLC compared to the microbial assay in a variety of circumstances is supported by a recent report from the World Health Organization (WHO), which provided that:

EDQM (European Directorate for the Quality of Medicines & HealthCare, the WHO custodian centre for antibiotics) has a long record of experience in monitoring the stability of official European Pharmacopeia (Ph. Eur.) reference standards for antibiotics. Due to the inherent variability of the microbiological assay methods, it was decided some years ago to replace them by stability indicating methods such as reverse phase high liquid chromatography (rp-HPLC) for monitoring the stability of the Ph. Eur. Reference standards. It was therefore believed to be of benefit to estimate the degradation at elevated temperature by rp-HPLC in addition to microbiological assays with the aim of collecting data for future replacement of the method . . .

Considering that the precision of the liquid chromatography method is much better than the precision of the microbiological assay, it is believed that with respect to the variability of these methods, any significant change in the impurity profile (by HPLC) will be detected ahead of any significant loss of potency.<sup>199</sup>

<sup>195</sup> VP July 20, 2010, Supp. at 3.

<sup>196</sup> USP Monograph of Vancomycin Hydrochloride, USP 23 - NF 18 (1995), page 1620.

<sup>197</sup> *Pharmacopeial Forum* 30(6) at 2055.

<sup>198</sup> Vila et al., *Analytical Methods for Vancomycin Determination in Biological Fluids and in Pharmaceuticals*, at 395-399 (2007).

<sup>199</sup> WHO/BS/10.2151. Collaborative Study for the Establishment of the Second International Standard for Vancomycin. Expert Committee on Biological Standardization, Geneva, 18 to 22 Oct 2010.

(f) The HPLC Method Together With the Dissolution Conditions Recommended by the Draft Vancomycin BE Guidance and the  $f_2$  Requirement Is Much More Stringent than the Use of the Microbiological Assay

The literature recognizes that, in contrast to the inherent variability of the microbiological assay methods mentioned above, the HPLC method is much more sensitive, accurate, precise, and robust.<sup>200</sup> The utility of the HPLC method has also been demonstrated during the method validations by DPQR. The sensitivity and wide linearity range of HPLC methods allows a single method to be applicable throughout the full time course of dissolution studies, including the early time periods recommended in the Draft Vancomycin BE Guidance. The accuracy and precision of HPLC methods ensure that the statistical analysis is meaningful. The specificity of HPLC methods also allows selective monitoring of components and dissolution homogeneity.<sup>201</sup>

In the Draft Vancomycin BE Guidance, the comparative dissolution conditions are clearly specified, emphasizing multiple media and multiple early time points. It provides that the dissolution data should be generated in three different media with USP Apparatus 1 (basket), rotating at 100 rpm, in a volume of 900 ml at 37° Celsius. Samples are to be taken at 5, 10, 20, 30, and 45 minutes, or as needed for profile comparison. This approach was taken because the HPLC method is sensitive, accurate and precise enough to detect the possible variation in the early time points, if any, and generates sufficient data for  $f_2$  statistical analysis, which measures the closeness between the two dissolution profiles.<sup>202</sup>

The Draft Vancomycin BE Guidance not only requires sampling at early time points (5, 10, and 20 minutes), but also requires dissolution to be performed in three dissolution media with a range of pH from 1.2 to 6.8 to precisely characterize the dissolution behavior and reveal any potential difference between the generic vancomycin HCl capsules and the RLD. Such difference, if any, will be detected by HPLC because of its high sensitivity, accuracy and precision. These data generated from the comparative dissolution studies then will be subjected to the  $f_2$  analysis to statistically demonstrate the equivalence between two dissolution profiles.

This stringent measurement of comparative dissolution, along with the quality control requirements set forth in the USP monograph, and the stability requirements recommended in relevant FDA guidances, ensure the product bioequivalence to the RLD.

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<sup>200</sup> Best, et al. "Chromatographic Separation of the Vancomycin Complex," at 15; Inman. "Determination of Vancomycin Related Substances by Gradient High-Performance Liquid Chromatography," at 363-372; Vila et al., "Analytical Methods for Vancomycin Determination in Biological Fluids and in Pharmaceuticals," at 395-399 (2007).

<sup>201</sup> The bioassay is a functional assay that considers the overall contribution of multiple components. If an individual component released heterogeneously (i.e., was not released at the same rate in each vancomycin product), the bioassay would not be able to detect the difference. In contrast, the HPLC method can reveal how much of each component is in the solution at a given time point if a heterogeneous dissolution happens.

<sup>202</sup> Tsong, Y., Sathe, P.M., Shah, V.P. *In Vitro Dissolution Profile Comparison. Encyclopedia of Biopharmaceutical Statistics: Second Edition* (April 2003).

FDA therefore concludes that the HPLC method is the most appropriate methodology available to assess the comparative dissolution of vancomycin capsule formulations.

(g) Appropriate Reference Standards for Use in the HPLC Analysis

As a general matter, HPLC methods are used in a comparative mode, which requires the use of reference standards for quantitation. The quality of reference standards is critical to ensuring accurate results, and these materials should be highly purified and well-characterized. As the Agency indicated in its draft guidance for industry on *Analytical Procedures and Method Validation*, reference standards from the USP/NF and other official sources do not require further characterization.<sup>203</sup> When there is no official source, a reference standard should be of the highest purity available and well-characterized to assure the purity, strength, identity, and quality of the material. Methods using noncompendial reference standards must incorporate any purity correction factor into calculations. Working reference standards are usually materials that were characterized and had their purity established against a primary reference standard. These sometimes are used in cases in which it is more cost effective to certify an in-house lot than to purchase USP reference materials for routine analysis.

Currently there are two USP reference standards available for vancomycin, Vancomycin HCl RS and Vancomycin B with Monodechlorovancomycin RS. The former is indicated for use in the Microbial Assay and the latter for the Limit of Monodechlorovancomycin by HPLC methodology in accordance with the USP monograph. Vancomycin B with Monodechlorovancomycin RS has weight/weight strength of Vancomycin B, which is the major component of Vancomycin, and is controlled by the Chromatographic Purity test in the same monograph. As a USP reference standard, it meets the requirements for the purity, strength, identity, and quality, and is intended to be used in HPLC analysis.

By using USP Vancomycin B with Monodechlorovancomycin RS, the HPLC method essentially quantifies vancomycin B as a surrogate to vancomycin. This approach is appropriate for use to evaluate comparative dissolution for the following reasons:

- Vancomycin B is the compound of greatest abundance in vancomycin.<sup>204</sup>
- Vancomycin B is the most critical component recognized by USP and specifically controlled by Chromatographic Purity test in the monograph.<sup>205</sup>
- The dominance of vancomycin B in vancomycin HCl has been consistently demonstrated at mid-90s percentage in the corresponding DMFs and ANDAs as a result of current purification technology.

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<sup>203</sup> Draft guidance for industry on *Analytical Procedures and Method Validation* (Aug. 2008).

<sup>204</sup> Best et al., *Chromatographic Separation of the Vancomycin Complex*, at 15.

<sup>205</sup> USP Monograph on Vancomycin Hydrochloride, USP 32 - NF 29, at 4565-66

Therefore, the Vancomycin B with Monodechlorovancomycin RS can be used without further qualification as a reference standard for quantitative analysis of vancomycin B by HPLC method to assess comparative dissolution.

While the USP Vancomycin HCl reference standard does not similarly quantify vancomycin B as a surrogate to vancomycin, the reference standard meets USP requirements for identity and quality, and may be used in the HPLC method for comparative dissolution assessment of vancomycin capsules. Because the HPLC method will assess both the RLD and the ANDA product against the same USP reference standard, it will reveal differences in dissolution between the RLD and proposed generic product as a result of formulation differences.

Based on the foregoing considerations, FDA has concluded that a fully validated HPLC method using USP reference standards (or other qualified reference standards), coupled with the dissolution requirements in the draft guidance and  $f_2$  criteria, is the appropriate methodology for assessing comparative dissolution of generic vancomycin capsules.<sup>206</sup>

7. Recent Articles by Omar Vesga and Colleagues Do Not Provide a Scientific Basis for Prohibiting Use of In Vitro Dissolution Data for Demonstrating Bioequivalence of Generic Vancomycin Capsules

You next cite two articles by Dr. Omar Vesga and his colleagues in which the authors claim that generic parenteral vancomycin products that pass in vitro potency assays have different in vivo performance from Vancocin. You claim that these papers indicate that there is no in vitro test or combination of in vitro tests that would ensure bioequivalence for generic vancomycin and reliably predict in vivo performance of the product.

These papers refer to the parenteral dosage forms of vancomycin, not the capsule solid oral dosage form at issue here. There are multiple ANDAs approved for the parenteral dosage form. As discussed below, FDA has considered these publications and your related arguments, and has determined that they provide no basis for rejecting use of the in vitro bioequivalence methodology set forth in the Draft Vancomycin BE Guidance to demonstrate bioequivalence of generic vancomycin capsules.<sup>207</sup>

(a) The 2009 Article Does Not Provide a Basis for Challenging FDA's Recommended In Vitro Dissolution Bioequivalence Methodology

First, you reference a 2009 paper published by Vesga and his research group entitled "*Application of microbiological assay to determine pharmaceutical equivalence of*

<sup>206</sup> Your suggestion that "in light of the inaccurate vancomycin dissolution data already received from the generic industry, to ensure the validation of any method proposed by a generic firm, FDA would need to independently validate the method in any event" is misplaced. VP July 20, 2010, Supp. at 12, n.41. FDA requires any ANDA sponsor to provide evidence that any methodology it uses to assess comparative dissolution has been validated. FDA evaluates the sufficiency of such evidence upon review of the individual ANDAs as part of the review process. Any deficiencies in the validation method would be identified at that time.

<sup>207</sup> Draft Vancomycin BE Guidance at 1-2.

*generic intravenous antibiotics.*<sup>208</sup> You note that despite the fact that “physicochemical methods [like the high performance liquid chromatographic (HPLC) method] are preferred over bioassays to determine [drug] concentration,” the authors of the article rejected use of such methods due to the fact that “significant variations in concentration are characteristic of vancomycin thereby making the ability to distinguish between concentration and potency integral to any analysis.”<sup>209</sup> Instead, you assert, the authors identified “a microbiological assay using large plates designed to determine potency and concentration of pharmaceutical-grade antibiotics for injection and a statistical method to assess the in vitro equivalence of generic products with respect to the innovator.”<sup>210</sup>

Although the authors identified this in vitro method to assess parenteral vancomycin, they (and you) argue that the method provides insufficient characterization of the vancomycin capsule due to the degradation products contained within that dosage form.<sup>211</sup> You assert that as a result of this limitation, and because “noncompedial” HPLC methods do not measure potency and the established USP bioassay does not measure concentration of degradation products, there is no feasible, sufficiently validated in vitro test or combination of tests that would ensure bioequivalence for generic vancomycin and reliably predict in vivo performance of the product.<sup>212</sup>

FDA agrees that the methods in that article are limited in that they only evaluate product potency and do not measure the purity of the antibiotics, and therefore, that the microbial assay developed would not be sufficient to provide the data necessary to demonstrate pharmaceutical quality, including purity. There is no support, however, for your claim that the article demonstrates that there is no feasible, sufficiently validated in vitro test or combination of tests that would ensure bioequivalence for generic vancomycin capsules and reliably predict in vivo performance of the product. Currently, as described above, vancomycin capsule ANDA applicants are requested to submit both microbial potency and HPLC data from validated methodologies. The measurement of comparative dissolution using a validated HPLC method, along with the quality control requirements including the microbial potency requirements set forth in the USP monographs for vancomycin, and the stability requirements recommended in relevant FDA guidances, ensure the product’s bioequivalence.

(b) The 2010 Article on Parenteral Vancomycin Does Not Provide a Basis for Challenging FDA’s Recommended In Vitro Dissolution Bioequivalence Methodology

You next address a 2010 article published by Vesga and his research group entitled “Generic Vancomycin Products Fail In Vivo Despite Being Pharmaceutical Equivalents

<sup>208</sup> Andres, F., Zuluaga et al., “Application of Microbiological Assay to Determine Pharmaceutical Equivalence of Generic Intravenous Antibiotics,” 2009, 9 *BMC Clinical Pharmacology* 1, 10 (Zuluaga Article).

<sup>209</sup> VP Nov. 21, 2011, Supp. at 2.

<sup>210</sup> Id. at 2.

<sup>211</sup> Id.

<sup>212</sup> Id. at 3.

of the Innovator.”<sup>213</sup> You assert that Vesga demonstrated that all of the generic products he evaluated failed to demonstrate in vivo equivalence despite the fact that each generic was “undistinguishable from the innovator based on concentration and potency, protein binding, in vitro antibacterial effect ... and serum pharmacokinetics.”<sup>214</sup> You cite four reasons identified by Vesga as causes of this failure to demonstrate the same in vivo performance: (1) antibacterials are secreted in nature and industrial production of an API involves complicated biosynthesis, purification, and manufacturing processes that are difficult to replicate; (2) two molecules can look similar without being identical and can display different biological effects; (3) generic manufacturers may not know the character of excipients employed by innovator manufacturers sufficient to avoid polymorphs; and (4) antimicrobials interact with the host and confront an invader organism, which creates a dynamic triangle with numerous possibilities of biologic variation.<sup>215</sup>

Vesga claims that his study demonstrated that parenteral vancomycin products that are equivalent in potency as measured by microbial assay demonstrated different in vivo performance in animal models. As a preliminary matter, the study was deficient in at least three ways. First, the study did not establish the chain of custody and storage conditions of the U.S.-sourced products used by Vesga.<sup>216</sup> If the products were stored inappropriately under conditions that could lead to the formation of impurities, then material used by the investigator would not be representative of the products in the U.S. marketplace. Second, the study did not characterize the purity of the products used in the study. If the purity of the products used in the study differed from those currently in the marketplace, then the study’s findings would not be relevant. Third, Vesga claims that crystalline degradation products (CDP-1) would be present at two to three times more in generic vancomycin parenteral products and that this could explain the in vivo findings of different potency. Vesga did not characterize the CDP-1 levels in the products used in his study, however, and, thus, his claim was unsupported.<sup>217</sup> Table 3 below contains the result of FDA’s Division of Pharmaceutical Analysis (DPA) laboratory evaluation of the purity of FDA-approved vancomycin injection products (including CDP-1 levels). FDA found that the maximum CDP in any tested product was 2%, and not at the levels Vesga speculated were present.<sup>218</sup>

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<sup>213</sup> Vesga, O. et al., “Generic Vancomycin Products Fail In Vivo Despite Being Pharmaceutical Equivalents of the Innovator,” 2010, 54 *Antimicrobial Agents and Chemotherapy* 8, 3271-1279 (Vesga Article).

<sup>214</sup> VP Nov. 21, 2011 Supp. at 4 (internal quotation to article omitted).

<sup>215</sup> VP Nov. 21, 2011, Supp. at 4-5.

<sup>216</sup> Vesga Article at 3272-3273.

<sup>217</sup> Id. at 3277-3278.

<sup>218</sup> CDER Division of Pharmaceutical Analysis, Memorandum re: Evaluation of Vancomycin Marketplace Products by UPLC-MS, at 2 (Sept. 19, 2011); CDER Division of Pharmaceutical Analysis, Memorandum re. Evaluation of Vancomycin in Marketplace Products, at 1 (April 15, 2011).

Source	% CDP-1 (BP method)	% CDP-1 (UPLC-UV method)	% CDP-1 (UPLC-MS method)
Sandoz	1.8	1.1	1.6
Baxter (lot 1)	0.6		
Baxter (lot 2)		0.3	0.7
Hospira	1.4	0.5	1.3
APP (lot 1)	1.2		
APP (lot 2)		ND	0.9
Bioniche (lot 1)	2.0		
Bioniche (lot 2)		0.2	1.4
Akorn (lot 1)	1.9		
Akorn (lot 2)		0.6	1.5

With respect to the particular points you raised regarding the Vesga article:

(1) FDA allows the API of generic products to be produced by different manufacturing processes, so the generic sponsor does not have to replicate the innovator's API manufacturing process.<sup>219</sup> However, the API used in generic products should meet the identity, potency, purity, and other quality standards as the API used in the brand product.<sup>220</sup>

(2) As discussed above, vancomycin can be specifically identified at the molecular level by current, validated analytical methods including the HPLC method.

(3) In the United States, the generic injectable vancomycin products must contain the same excipients in the same amount as the RLD product,<sup>221</sup> so this point is not relevant.

(4) There is biologic variation, but this variation affects both the brand and the generic product equally. For example, if the organism changes the host, both the brand and generic antibiotics are exposed to the changed host environment and would be equally affected by the same biological variability because they provide equivalent exposure of the same active ingredient to the host and organism.

Thus these differences do not support your argument that in vivo efficacy studies for generic vancomycin capsules are necessary to demonstrate bioequivalence.

<sup>219</sup> See generally, 21 U.S.C. 355(j)(2) (does not require demonstration of same manufacturing process as reference listed drug); 21 CFR 314.94(a)(9)(i) (requiring information related to manufacture of ANDA product).

<sup>220</sup> 21 U.S.C. 355(j)(2)(A)(ii)(I) (same active ingredient requirement).

<sup>221</sup> 21 CFR 314.94(a)(9)(iii).

(c) The Vesga Article Does Not Demonstrate That Potential Manufacturing Differences Alter In Vivo Performance Such That In Vivo Data Are Necessary to Demonstrate Bioequivalence

You next assert that FDA's current recommendation that generic vancomycin capsules need only demonstrate Q1/Q2 sameness fails to adequately account for potential wide variation in manufacturing and formulation conditions, which you refer to inaccurately as "Q3" sameness. In support of this position, you claim that Vesga has demonstrated that manufacturers that are not required to copy the manufacturing conditions of the innovator can alter the in vivo performance of vancomycin, and that current in vitro testing methods are insensitive to such manufacturing-associated differences.<sup>222</sup>

Your claims about different manufacturing processes are not relevant to Q3 equivalence. As discussed above, "Q3" sameness generally means the formulations have the same structural characteristics in terms of components, concentration, and microstructure.<sup>223</sup> The products evaluated in this article were all solutions that are, by definition, Q3 equivalent. Solutions of dissolved drugs have no specific structural arrangement of matter or microstructure. Once a drug is dissolved, there is no trace of the solid structure the material had before it dissolved. The Q3 concept is intended to describe differences in solid structure and thus is not relevant to solutions.

For generic vancomycin capsules, we previously have discussed in section II.B.4 above, why Q3 sameness is not required to demonstrate bioequivalence. The Vesga Article's concerns about manufacturing processes for the parenteral products are related to the potential for different manufacturing processes to produce different impurities. As discussed above, chromatographic methods can characterize the impurities present in vancomycin capsules and thus, would identify whether a difference in manufacturing process had a significant impact on product impurities.

You also argue that in light of the Vesga and Zuluaga Articles, FDA must provide a scientific rationale for its currently recommended in vitro dissolution methodology and assess (1) the potential insensitivity of the recommended methodology with respect to product purity of the API used in parenteral formulations; (2) the "wholly unstudied and untested" impact of small deviations in excipient profiles on generic products; (3) the potential impact of differences in degradation profiles as a function of process and formulation differences, and "what, if any, data support OGD's conclusion that such differences would not result in in vivo performance differences when generics need only meet [current good manufacturing practices]."<sup>224</sup>

<sup>222</sup> VP Nov. 21, 2011, Supp. at 4.

<sup>223</sup> Wilkin, Jonathan, Presentation: *The Pursuit of Alternative Methodologies For Demonstrating Bioequivalence for Generic Topical Dermatologic Drug Products: DPK, Q3, Cakes, and 2 Pls.*

<sup>224</sup> VP Nov. 21, 2011, Supp. at 6.

FDA permits generic versions of Vancocin Capsules to demonstrate bioequivalence using an in vitro dissolution test if they are Q1/Q2 the same as Vancocin (or can demonstrate that differences in excipients do not affect the safety or effectiveness of the product), and meet appropriate chemistry, manufacturing and control quality standards. These quality standards include both antimicrobial potency and standards for ensuring purity using HPLC methods. The Vesga and Zuluaga Articles do not provide evidence that products with equivalent potency and purity would behave differently in vivo; they only considered potency testing and did not characterize the purity of the products used in the study.<sup>225</sup>

(d) The ACPS Does Not Need To Be Reconvened To Consider the Vesga and Zuluaga Articles and/or Q3 Sameness

You assert that members of the August 2009 ACPS that considered use of an in vitro bioequivalence methodology for vancomycin expressed concern that tight manufacturing controls and more rigorous manufacturing site inspections should be conducted for generic vancomycin products as compared to other generic products. In light of the members' concerns and Vesga's work (which was not considered by the Committee), you claim that a new advisory committee meeting that includes Dr. Vesga is necessary to consider (1) whether Q3 sameness should be required; and (2) the impact of Vesga's "evidence" that in vivo performance cannot be reliably predicted by existing in vitro tests.<sup>226</sup>

At the 2009 ACPS meeting, Committee members mentioned the importance of manufacturing controls, inspections, and postmarketing evaluations, but they did not indicate that vancomycin should be subject to more rigorous evaluation than other products.<sup>227</sup>

Of note, representatives of ViroPharma presented the "Q3" issue at the August 2009 meeting.<sup>228</sup> The Committee discussed but did not endorse your recommendation that Q3 sameness be required for demonstrating vancomycin bioequivalence using in vitro data.<sup>229</sup> Further, the Vesga and Zuluaga Articles do not provide the complete characterization of the purity of the products studied that would be needed as an initial matter to evaluate their conclusions, nor does either Article present any issues that support the need for an additional advisory committee meeting.

<sup>225</sup> Generic and reference products are permitted to have some differences in impurities. As part of the ANDA submission, the generic sponsor provides information on the purity of its product. In the ANDA review process these impurity levels are reviewed for acceptability based in part on what is known about the purity of the reference product. In addition, compendial (USP) standards are also considered and an overall conclusion about the acceptable purity for generic product is made. See the guidance for industry on *ANDAs: Impurities in Drug Products* (Nov. 2010).

<sup>226</sup> VP Nov. 21, 2011, Supp. at 7.

<sup>227</sup> 2009 ACPS Tr. at 144-152.

<sup>228</sup> ViroPharma Slide Presentation, at 19, 31, Aug. 4, 2009 ACPS Meeting, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/UCM179424.pdf>.

<sup>229</sup> See, e.g., 2009 ACPS Tr. at 161-166; 219-20, 298 ("I find that [Q3] sameness an interesting idea, but I'm not sure the case was fully made") (comment of Dr. Nemhhard).

You thus have not demonstrated that there is a need for the ACPS to consider any of these issues, or to reconsider its 2009 unanimous endorsement of the bioequivalence recommendation in the Draft Vancomycin BE Guidance.

- (e) Your Request That the Agency Take Into Special Account Risks That May Be Posed to Patients By Non-Bioequivalent Generic Vancomycin Capsules Before Permitting In Vitro Data to Demonstrate Bioequivalence Disregards the Statutory Requirements of Section 505(j)

You refer to comments submitted to the citizen petition docket by members of the scientific and medical communities and to the World Health Organization's position on consideration of patient populations. You assert that the Agency must take into account the severity of the risks to patients that may be posed by substituting inequivalent generic vancomycin capsules before permitting in vitro data to demonstrate bioequivalence.

FDA will not approve a generic drug unless it determines that the drug can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. As such, we apply the most appropriate scientific standards (including the identification of recommended bioequivalence studies) to all generic drugs to ensure that only drugs that meet this rigorous standard are approved. FDA does not lower the criteria for ANDA approval (including the standards for finding sameness of generic and reference products), for those drugs where inequivalence is not expected to have a significant impact on patients. The converse is also true — the approval standards are sufficiently rigorous and robust that they do not need to be raised even where the patient populations are particularly sensitive or the product is intended to treat a life-threatening condition.

Regarding the sufficiency of in vitro equivalence testing to evaluate the bioequivalence of generic oral capsule vancomycin products to the reference product, this was the primary focus of the 2009 meeting of FDA's Advisory Committee for Pharmaceutical Science. Their unanimous conclusion was that in vitro testing was the most appropriate method for assessing bioequivalence for oral vancomycin products.

#### 8. ANDA Applicants Are Not Required To Submit "Failed" Bioequivalence Studies

You next assert that FDA must require all ANDA applicants for generic vancomycin to submit all bioequivalence studies they have conducted in order to prevent fraud on the Agency and to avoid "gerrymandering" of favorable dissolution results, citing the recently amended 21 CFR 314.94(a)(7).<sup>230</sup> As of 2009, this regulation requires ANDA applicants to submit all bioequivalence studies conducted on a drug product formulation for which approval is sought. But FDA expressly declined to apply the rule retroactively. As stated in the preamble to the final rule: "[w]ith respect to ANDAs, amendments or

<sup>230</sup> VP Draft Guidance Resp. at 49; VP Dec. 2, 2009, Supp. at 6; VP June 25, 2010, Supp. at 10.

supplements submitted prior to [July 15, 2009], applicants are not required to report additional BE studies that were conducted with their applications.”<sup>231</sup>

C. FDA Has the Legal Authority to Accept In Vitro Dissolution Data To Establish Bioequivalence for Generic Vancomycin

In addition to your scientific challenges to the vancomycin bioequivalence recommendation, you dispute FDA’s legal authority to accept in vitro data to demonstrate bioequivalence of generic vancomycin products on myriad grounds. None of your legal arguments has merit, as we explain in detail below.

1. The Draft Vancomycin BE Guidance In Vitro Methodology Complies With the Legal Requirement That an Applicant Use the Most Accurate, Sensitive and Reproducible Methodology Available

As described in detail in section I.B., Congress has given FDA broad authority to determine the appropriate method by which an ANDA applicant can establish bioequivalence for generic vancomycin (section 505(j)(8) of the FD&C Act). This authority is reflected in various provisions of the statute (e.g., section 505(j)(7)(a)(iii)), and serves as the cornerstone of bioequivalence regulations set forth in section 320.24(a): “FDA may require in vivo or in vitro testing, or both, to ... establish the bioequivalence of specific drug products.” Subsection 320.24(b) outlines different methods by which bioequivalence may be demonstrated, and permits, in addition to the delineated methods, “[a]ny other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence.”<sup>232</sup>

You assert that, as a legal matter, an ANDA applicant for vancomycin capsules must provide data from clinical endpoint bioequivalence studies, rather than in vitro data, because such studies are listed higher on the descending scale of acceptable bioequivalence methodologies set forth in 21 CFR 320.24(b), and otherwise are “feasible.”<sup>233</sup> Section 320.24(b) sets forth methodologies in descending order of preference as a general matter. The ultimate selection of the appropriate bioequivalence method is determined on a case-by-case basis, however, and “*depends upon the purpose of the study, the analytical methods available, and the nature of the drug product.*”<sup>234</sup>

<sup>231</sup> *Requirements for Submission of Bioequivalence Data; Final Rule*, 74 FR 2849, 2858 (Jan. 16, 2009).

<sup>232</sup> 21 CFR 320.24(e).

<sup>233</sup> VP Oct. 6, 2009, Supp. at 14, n.63.

<sup>234</sup> 21 CFR 320.24(a) (emphasis added). See also *Abbreviated New Drug Application Regulations: Final Rule*, 57 FR 17950, 17972 (April 28, 1992) (“[t]he preferred method for establishment of bioequivalence ... is determined on a case-by-case basis, depending on the drug under study”).

FDA has determined, for the reasons set forth above in section II.A and C, that the most accurate, sensitive, and reproducible approach available for demonstrating vancomycin capsule bioequivalence is one using in vitro dissolution data, and not clinical study data, which is the least sensitive for this product. This decision is fully consistent with the regulations.

2. Section 320.24(b)(1)(ii) Does Not Provide the Sole Basis for Permitting In Vitro Data To Demonstrate Bioequivalence

You assert that subsection 320.24(b)(1)(ii), which describes a bioequivalence approach in which in vitro data is correlated with in vivo data, is the exclusive circumstance in which FDA may accept in vitro studies to establish bioequivalence.<sup>235</sup> You appear to be invoking the interpretative maxim *expressio unius est exclusio alterius*, which provides that the expression of one item of an associated group or series should be interpreted to exclude another left unmentioned. As courts have noted, however, this canon does not apply when the Agency has indicated, as it clearly has here, that the enumeration is not intended to be exclusive.<sup>236</sup> Subsection 320.24(e) expressly provides that bioequivalence may be demonstrated by “[a]ny other approach deemed adequate by FDA to . . . establish bioequivalence” in addition to those set out in subsections 320.24(b)-(d).<sup>237</sup> Your attempt to narrow section 320.24 therefore is unavailing, and more generally is inconsistent with the broad discretion granted FDA to determine an appropriate bioequivalence methodology.<sup>238</sup>

3. There Is No Default Requirement for In Vivo Data to Demonstrate Bioequivalence

You next argue that the bioequivalence regulations “establish a general rule in 21 CFR 320.21 that to demonstrate bioequivalence ANDA sponsors must submit information obtained in vivo, unless a sponsor can meet the criteria for a waiver set forth in 21 CFR 320.22.”<sup>239</sup> Your argument lacks merit because there is no such “general rule” requiring in vivo data, as is evident from the plain language of the bioequivalence regulations. Section 320.1(f) defines “[b]ioequivalence requirement” as “a requirement imposed by the Food and Drug Administration for in vitro and/or in vivo testing of specified drug products which must be satisfied as a condition of marketing.”<sup>240</sup> Section 320.24(a) provides that “FDA may require in vivo or in vitro testing, or both, to measure the

<sup>235</sup> VP Supp. Oct. 6, 2009, Supp. at 12; VP Draft BE Guidance Resp. at 8.

<sup>236</sup> *Ohio v. U.S. Dep't of the Interior*, 880 F.2d 432, 446-47 (D.C. Cir. 1989) (rejecting invocation of maxim where Congress expressly noted related list included but was not limited to certain elements of damage awards).

<sup>237</sup> 21 CFR 320.24(e). You assert that 320.24(e) is limited to special in vivo situations involving animal drugs or isotopically labeled drugs, based on statements in a preamble to the 1977 regulations. VP July 25, 2008, Supp. at 6. The plain language of this provision — “[a]ny other approach deemed adequate by FDA” — cannot reasonably be construed to be so restricted, however. *Thomas Jefferson University v. Shalala*, 512 U.S. 504, 515 (1994) (rejecting petitioner’s effort to limit plain language of broad regulation).

<sup>238</sup> VP Supp. Dec. 2, 2009, at 4. For these reasons, your related assertion that the regulations must be amended for an applicant to rely solely on in vitro dissolution studies is misplaced.

<sup>239</sup> VP July 25, 2008, Supp. at 1-2.

<sup>240</sup> 21 CFR 320.1(f).

bioavailability of a drug product or establish the bioequivalence of specific drug products.”<sup>241</sup> Section 320.24(b) then lists methodologies — in vivo, in vitro, and “any other approach deemed adequate by FDA” — to measure bioequivalence. These provisions are consistent with the discretion accorded the Agency by Congress in section 505(j)(8)(C) of the FD&C Act (FDA “may establish alternative, scientifically valid methods to show bioequivalence” for drug products, including vancomycin).

Your related assertion — that FDA’s acceptance of in vitro data to demonstrate bioequivalence under its section 320.24 authority renders section 320.22 superfluous — is unavailing. If FDA establishes an in vivo data requirement for a proposed generic product, then subsection 320.21(b)(2) permits an ANDA applicant to seek waiver of such a requirement in the manner specified in subsection 320.22.<sup>242</sup> If FDA does not require in vivo data to demonstrate bioequivalence in the first instance, then sections 320.21(b)(2) and 320.22 do not apply. In other words, the waiver procedure set forth in section 320.22 applies only after FDA determines that in vivo data should be submitted.<sup>243</sup>

Notably, the text of section 320.21 (“Requirements for submission of bioavailability and bioequivalence data”) itself, which you cite as the authority for your position, evidences the regulation’s limited function. Section 320.21(a) pertains to the requirement for NDA applicants to demonstrate bioavailability of a proposed new drug product, and requires such an applicant to provide “(1) [e]vidence measuring the in vivo bioavailability of the drug product that is the subject of the application; or (2) [i]nformation to permit FDA to waive the submission of evidence measuring in vivo bioavailability” (emphasis added).<sup>244</sup> Section 320.21(b), by contrast, pertains to the ANDA requirement of demonstrating bioequivalence, and does not contain an in vivo data requirement. Rather, the bioequivalence data provision requires an ANDA applicant to submit “[e]vidence demonstrating that the drug product that is the subject of the abbreviated new drug application is bioequivalent to the reference listed drug [...], or (2) [i]nformation to show that the drug product is bioequivalent to the reference listed drug which would permit FDA to waive the submission of evidence demonstrating in vivo bioequivalence as provided in paragraph (f) of this section.” Sub-paragraph (2) requires conformance with section 320.22 when an applicant seeks waiver of an Agency-imposed in vivo data requirement. Your interpretation, which would require clinical testing of patients in all cases unless the narrow exceptions set forth in section 320.22 are met, also runs counter to the guiding principle, articulated in section 320.25, that “no unnecessary human research should be done.”<sup>245</sup>

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<sup>241</sup> 21 CFR 320.24(a).

<sup>242</sup> 21 CFR 320.21(b)(2) and (f).

<sup>243</sup> For these reasons, your assertions that FDA seeks to rely on section 320.24 as an authority for waiver of an in vivo data requirement for vancomycin, and for other recent generic drug approvals also are unavailing. VP July 25, 2008, Supp. at 3, 5-7.

<sup>244</sup> 21 CFR 320.21(a).

<sup>245</sup> 21 CFR 320.25(a) (entitled “Guiding Principles”) (“The basic principle in an in vivo bioavailability study is that no unnecessary human research should be done”).

In addition, the regulatory history shows that FDA has not established a default in vivo data requirement. Indeed, the history makes clear that FDA intended to exercise the full scope of its statutory discretion to determine the appropriate bioequivalence methodology. In the preamble to the 1992 final rule, FDA explained that, depending upon the drug, the Agency would determine the appropriate bioequivalence methodology on a case-by-case basis:

Bioequivalence can be established by pharmacodynamic measurement as well as by in vitro techniques and bioequivalence studies with clinical endpoints. The preferred method for establishment of bioequivalence . . . is determined on a case-by-case basis, depending on the drug under study.<sup>246</sup>

FDA pointed out that Congress had authorized both in vivo and in vitro methods to establish bioequivalence: “[h]ad Congress intended to require only direct measurements of the rate and extent of absorption in the human body, it would not have also permitted in vitro studies to satisfy the bioequivalence requirements.”<sup>247</sup> In the same preamble, FDA rejected a suggestion that the Agency amend a separate regulation — subsection 314.94(a)(7)(iii), which sets forth the required contents of an ANDA — to state that waivers from an in vivo bioequivalence requirement are available under 21 CFR § 320.22.<sup>248</sup> The Agency reasoned that “[s]ection 314.94(a)(7), generally, and § 314.94(a)(7)(iii), specifically, do not require in vivo bioequivalence.”<sup>249</sup> FDA further noted, “[i]nformation to show bioequivalence may, depending upon the drug product, come from an in vivo or an in vitro study.”<sup>250</sup>

You cite language from the 1989 preamble to the proposed rule regarding FDA’s intent to eliminate a provision for a blanket waiver of in vivo bioavailability for generic drugs, the former section 320.22(d)(5).<sup>251</sup> FDA sought to remove this blanket waiver because it “ha[d] no evidence to show that in vitro data alone are regularly sufficient to assure bioequivalence.”<sup>252</sup> Contrary to your contention, FDA’s elimination of a blanket waiver did not “explicitly relinquish” the Agency’s statutory discretion to determine the appropriate bioequivalence methodology on a case-by-case basis.

To further support your argument, you similarly cite FDA’s elimination of an automatic waiver of in vivo tests for “an oral dosage form that is not intended for systemic absorption.”<sup>253</sup> FDA explained in the preamble to the 1992 final rule that it removed the automatic waiver because in vivo tests “may be required for certain products.”<sup>254</sup> The Agency reasoned that “requests for waiver of in vivo . . . bioequivalence for these products need to be reviewed on a case-by-case basis,” and noted that “the regulation

<sup>246</sup> *Abbreviated New Drug Application Regulations: Final Rule*, 57 FR at 17972 (emphasis added).

<sup>247</sup> *Id.*

<sup>248</sup> *Id.* at 17960.

<sup>249</sup> *Id.*

<sup>250</sup> *Id.*

<sup>251</sup> VP July 25, 2008, Supp. at 6, n.18 (citing 21 CFR 320.22(d)(5) (1983)).

<sup>252</sup> *Abbreviated New Drug Application Regulations, Proposed Rule*, 54 FR at 28912 (emphasis added).

<sup>253</sup> VP July 25, 2008, Supp. at 6, n.18; VP Draft Guidance Resp. at 40.

<sup>254</sup> *Abbreviated New Drug Application Regulations: Final Rule*, 57 FR at 17975.

does permit applicants to request a waiver of the requirement for the submission of evidence in the form of in vivo . . . bioequivalence data provided the product meets the criteria in § 320.22.”<sup>255</sup> This language describes applicants’ ability to request waivers under section 320.22, but does not “explicitly relinquish” FDA’s statutory discretion to make independent determinations of the appropriate bioequivalence methodology pursuant to subsection 320.24(a) in the first instance.

You also seek to draw support from FDA’s correction, in subsection 320.21(f), of an erroneous reference to section 320.24 instead of section 320.22.<sup>256</sup> Subsection 320.21(f) originally read as follows: “[i]nformation to permit FDA to waive the submission of evidence . . . demonstrating the in vivo bioequivalence shall meet the criteria set forth in § 320.24.” In 1998, FDA amended this provision to change the section referenced: subsection 320.21(f) now refers to section 320.22. FDA explained that “Section 320.21(f) inaccurately includes a reference to criteria set forth in § 320.24 as containing information under which FDA could waive the requirement for submission of evidence demonstrating in vivo . . . bioequivalence.”<sup>257</sup> This correction does not have the significance that you claim. FDA does not dispute that section 320.22 contains criteria relating to waivers that an applicant may request, and that those criteria are what subsection 320.21(f) was intended to reference. But the correction did not affect subsection 320.24(a), which does not pertain to waivers, but rather, sets out FDA’s authority for determining what type of data is required for demonstrating bioequivalence in the first instance.

Finally, there is no merit to your claim that FDA cannot allow an ANDA applicant to demonstrate bioequivalence for vancomycin through in vitro data without receiving a waiver under the authority of the BCS Guidance.<sup>258</sup> As discussed in above, FDA is not requiring ANDA applicants for generic vancomycin to submit in vivo data, so they do not need to request a waiver for such a requirement. Even if FDA were to impose an in vivo data requirement for which a generic applicant might seek a waiver, the BCS Guidance does not provide the authority for waivers of in vivo data, nor does it describe the totality of the circumstances in which such waivers may be available. It merely sets out the Agency’s thinking on some scenarios in which such waivers may be appropriate. Your related suggestion that the BCS Guidance sets forth an exhaustive list of the circumstances in which a waiver of in vivo bioequivalence is available is contrary to the clear language of the statute, which provides that FDA has broad discretion to establish bioequivalence standards.<sup>259</sup>

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<sup>255</sup> Id.

<sup>256</sup> VP July 25, 2008, Supp. at 6-7.

<sup>257</sup> *Bioavailability and Bioequivalence Requirements: Abbreviated Applications; Proposed Revisions*, 63 FR 64222, 64223 (Nov. 19, 1998).

<sup>258</sup> VP Draft Guidance Resp. at 19-20.

<sup>259</sup> Section 505(j)(8)(C) of the FD&C Act. See also 21 CFR 320.24(a).

4. FDA Need Not Amend Section 320.22 To Consider Q1/Q2 Sameness in Determining Bioequivalence

You next claim that FDA can only consider Q1/Q2 sameness in bioequivalence determinations in the context of a waiver of an in vivo data requirement for the classes of products specified in 21 CFR 320.22(d), which subsection involves consideration of inactive ingredient similarity and/or sameness. Your argument misconstrues FDA's authority to make bioequivalence determinations. FDA's discretion to determine the appropriate bioequivalence methodology for a product is authorized by the statute and section 320.24 of the regulations, not sections 320.21 and 320.22. As described above, section 320.22(d) is a narrow provision that provides a process by which applicants can apply for a waiver of an in vivo data requirement that FDA otherwise has imposed on a specific product or product. The specific provision that you cite, 320.22(d)(3), concerns oral solutions and involves consideration of inactive ingredient sameness. Citation to inactive ingredient sameness here does not preclude FDA's consideration of Q1/Q2 sameness in the context of a 320.24(a) determination. Nor is FDA, as you contend, attempting to amend 320.22(d)(3) to include products like vancomycin by permitting the use of Q1/Q2 sameness to support bioequivalence of generic vancomycin. Section 320.22 simply is not relevant to the recommended in vitro dissolution bioequivalence methodology for generic vancomycin.

5. FDA Is Not Precluded From Considering Exceptions to the Q1/Q2 Requirement

In the Draft Vancomycin BE Guidance, FDA indicates that it may permit in vitro dissolution data to demonstrate bioequivalence for products that are not Q1/Q2, if the applicant can demonstrate that the differences in excipients will not affect the safety or efficacy of the product. You maintain that accepting such evidence would constitute rulemaking without giving the public notice and an opportunity to comment, citing 21 CFR 314.94(a)(9)(iii)-(v), which relate to inactive ingredients in proposed generic products.<sup>260</sup>

Some statutory and regulatory background is necessary to address your argument. Section 505(j)(2) of the FD&C Act requires an ANDA applicant to submit information related to the inactive ingredients in a proposed generic product.<sup>261</sup> Consistent with the statute, subsection 314.94(a)(9)(ii) provides that "[u]nless otherwise stated in paragraphs (a)(9)(iii) through (a)(9)(v) of this section, an applicant shall identify and characterize the inactive ingredients in the proposed drug product."<sup>262</sup> This subsection also requires an applicant to "provide information demonstrating that such inactive ingredients do not affect the safety or efficacy of the proposed drug product."<sup>263</sup>

<sup>260</sup> VP Mar. 25, 2010, Supp. at 27.

<sup>261</sup> 21 U.S.C. 355(j)(2)(vi).

<sup>262</sup> 21 CFR 314.94(a)(9)(ii).

<sup>263</sup> Id.

In subsections 314.94(a)(9)(iii)-(a)(9)(v) (relating to parenteral, ophthalmic, and otic dosage forms, respectively), FDA has more stringent limitations on inactive ingredients to account for the fact that each of these drug products represents an individual pharmaceutical system with its own characteristics and requirements, and that inactive ingredients are added to maintain these systems.<sup>264</sup> FDA “presume[s] different inactive ingredients in these products unsafe unless the applicant can rebut the presumption by demonstrating that the different inactive ingredient will not affect the safety of its proposed product.”<sup>265</sup> For example, subsection 314.94(a)(9)(iii) provides that “a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug,” but that “an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.”<sup>266</sup>

You assert that the option set out in the Draft Vancomycin BE Guidance for ANDA applicants to use in vitro data for non-Q1/Q2 products if the applicant can show the differences do not affect safety or effectiveness, should not be available to ANDA applicants until FDA amends section 314.94(a)(9) to include a Q1/Q2 sameness requirement for products like vancomycin.<sup>267</sup> But subsection 314.94(a)(9) is not related to what is permissible in demonstrating bioequivalence. Instead, subsections 314.94(a)(9)(iii)-(v) reflect the Agency’s determination of what generally is required in inactive ingredients to ensure safe use of certain products due to the fact that those products function as individual pharmaceutical systems. That context is completely different from the demonstration of bioequivalence using in vitro data.

You also assert that FDA may not consider in vitro data for products that are not Q1/Q2 because the August 2009 ACPS discussed but did not formally vote on this question.<sup>268</sup> Although FDA acknowledges the fundamentally important role that advisory committees play in the regulatory approval process, FDA is not limited to accepting only data endorsed by an advisory committee. As the advisory committee regulations explicitly state, “[t]he Commissioner has sole discretion concerning action to be taken and policy to

<sup>264</sup> *Abbreviated New Drug Applications; Proposed Rule*, 54 FR at 28883-884.

<sup>265</sup> *Id.* at 28884.

<sup>266</sup> *Id.* See also 21 CFR 314.94(a)(9)(iv) (“a drug product intended for ophthalmic or otic use shall contain the same inactive ingredients and in the same concentration as the reference listed drug ... However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product, except that, in a product intended for ophthalmic use, an applicant may not change a buffer or substance to adjust tonicity for the purpose of claiming a therapeutic advantage over or difference from the listed drug...”); 21 CFR 314.94(a)(9)(v) (“[g]enerally, a drug product intended for topical use, solutions for aerosolization or nebulization, and nasal solutions shall contain the same inactive ingredients as the reference listed drug. However, an abbreviated application may include different inactive ingredients provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product”).

<sup>267</sup> VP Mar. 25, 2010, Supp. at 27.

<sup>268</sup> VP Dec. 2, 2009, Supp. at 4-5; VP Mar. 25, 2010, Supp. at 27 n.137.

be expressed on any matter considered by an advisory committee.”<sup>269</sup> FDA is not bound by an advisory committee recommendation, and is empowered to act even in the absence of an advisory committee vote.

#### 6. FDA Has Authority To Waive an In Vivo Bioequivalence Data Requirement

As described in detail above, FDA has the legal authority to establish bioequivalence standards for drug products, and in particular, to determine that in vitro dissolution studies may be submitted to establish bioequivalence of a generic drug product. Neither the statute nor the regulations impose a default in vivo data requirement for demonstrating bioequivalence, and thus, an ANDA applicant need not secure a waiver prior to the Agency accepting in vitro studies, unless FDA has determined that in vivo data is required. For generic vancomycin capsules, FDA has concluded that ANDA applicants may submit in vitro data under the specifications set forth above to establish bioequivalence for vancomycin capsules. An applicant therefore need not secure a waiver under section 320.22 to establish bioequivalence using in vitro dissolution data.

Even if there were a “default” in vivo data requirement for all ANDAs so that a waiver under section 320.22 were required, FDA has determined that the Agency would waive such a requirement for generic vancomycin capsule applicants that meet the criteria for in vitro data set forth above under 21 CFR 320.22(e). Section 320.22(e) provides that “FDA, for good cause, may waive a requirement for the submission of evidence of . . . bioequivalence if waiver is compatible with the protection of the public health.”<sup>270</sup> FDA concludes that such a waiver would be for good cause and compatible with the public health for generic vancomycin capsules for several reasons. As discussed above, vancomycin is one of only two FDA-approved treatments for the fast-moving, life-threatening colitis associated with CDAD. As detailed in your citizen petition supplements,<sup>271</sup> increased incidence of CDAD infections as well as more severe instances of the disease have been extensively reported in the medical literature and general media.<sup>272</sup> Medical literature also indicates that in light of the high demand and high cost of Vancocin Capsules, doctors and hospitals have begun administering vancomycin parenteral solution to patients orally to treat CDAD.<sup>273</sup> This formulation has never been approved for oral use or for use in this fashion, and thus raises potential public health concerns including a risk of dosage errors. The availability of safe and effective generic

<sup>269</sup> 21 CFR 14.5(b).

<sup>270</sup> 21 CFR 320.22(e).

<sup>271</sup> VP June 30, 2006, Supp. at 10-14.

<sup>272</sup> Hall, A.J., Curns, L.C. McDonald, U.D. Parashar, B.A. Lopman, Centers for Disease Control and Prevention, “Abstract: Gastroenteritis Deaths on the Rise in the United States: The Emerging Roles of Clostridium difficile and Norovirus” at 190 (presented at 2012 International Conference on Emerging Infectious Diseases), available at [http://www.iceid.org/images/iceid\\_2012\\_finalprogram\\_final.pdf](http://www.iceid.org/images/iceid_2012_finalprogram_final.pdf).

<sup>273</sup> Can. J. Hosp. Pharm. 2010 Sep-Oct; 63(5): 366–372; see also Generic Pharmaceutical Association, Presentation, Aug. 4, 2009 ACPS Meeting, available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/UCM179425.pdf>.

vancomycin capsules would mitigate these concerns consistent with the fundamental purposes of Hatch-Waxman: to make available to consumers safe and effective generic drug products.<sup>274</sup>

7. The FD&C Act Does Not Require That Individual Bioequivalence Recommendations Be Published in the Orange Book When an RLD Is Listed

You contend that subsection 505(j)(7)(A)(i)(III) of the FD&C Act requires FDA to publish a specific bioequivalence requirement for all listed drugs prior to (and irrespective of the likelihood of approval of) a pharmaceutically equivalent second drug, and that the Agency's failure to do so for vancomycin capsules violated the FD&C Act.<sup>275</sup> Your contention is unfounded. Section 505(j)(7)(A)(i) provides that "the Secretary shall publish and make available to the public" three sets of information: "(I) a list in alphabetical order of the official and proprietary name of each drug which has been approved for safety and effectiveness under subsection (c) ...; (II) the date of approval if the drug is approved after 1981 and the number of the application which was approved; and (III) whether in vitro or in vivo bioequivalence studies, or both such studies, are required for applications filed under this subsection which will refer to the drug published."<sup>276</sup> The Orange Book lists approved drugs together with the approval date and the application number at the time the NDA is approved or shortly thereafter.<sup>277</sup> The Agency fulfills the third prong of this statutory directive by including on the list of approved products a "therapeutic equivalence" code for each product once another product that is pharmaceutically equivalent to the listed product is approved.<sup>278</sup> These therapeutic equivalence codes indicate the type of bioequivalence data FDA required prior to approving the therapeutically equivalent product(s).<sup>279</sup>

<sup>274</sup> *Teva Pharm. Indus. v. Crawford*, 410 F.3d at 55; H.R. Rep. No. 98-857(I), at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647, 2647-48 (stating that one of the purposes of the legislation is "to make available more low cost generic drugs"). Such a waiver also would promote FDA's general mission to protect the public health by ensuring only safe and effective products are marketed, and to ensure that the financial interests of consumers are protected. *U.S. v. Lane Labs-USA Inc.*, 427 F.3d 219, 227 (3d Cir. 2005) ("[t]he FDCA and its legislative history make it clear that Congress intended the statute to protect the financial interests of consumers as well their health").

<sup>275</sup> VP Dec. 22, 2010, Supp. at 1-2.

<sup>276</sup> 21 U.S.C. 355(j)(7)(A)(i)(III).

<sup>277</sup> 21 CFR 314.3(b).

<sup>278</sup> See 21 CFR 320.24(a) ("Information on bioequivalence requirements for specific products is included in the current edition of FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" and any current supplement to the publication"); *Abbreviated New Drug Application Regulations, Proposed Rule*, 54 FR at 28911 ("FDA satisfies [the section 505(j)(7)(A)(i)(III)] requirement through the use of therapeutic equivalence codes" in the Orange Book). Two products are considered "pharmaceutically equivalent" if they contain the same active ingredient(s), are of the same dosage form, route of administration, and are identical in strength or concentration (21 CFR 320.1(c)); *Orange Book*, introduction at v. Two products are considered "therapeutically equivalent" only if they are pharmaceutically equivalent and if they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the label. *Orange Book*, introduction at iv.

<sup>279</sup> As described in the *Orange Book* Introduction, "[t]he coding system for therapeutic equivalence evaluations is constructed to allow users to determine quickly whether the Agency has evaluated a

You assert that FDA must publish information regarding bioequivalence requirements at the same time that the RLD is listed.<sup>280</sup> The plain language of the statute does not mandate publication of this information at the time of the RLD listing, nor does it otherwise direct when FDA must fulfill this requirement. Notably, none of the courts that have considered FDA's compliance with section 505(j)(7)(A)(i)(III) have construed the statute in the manner you suggest or otherwise have found any legal deficiency in FDA's practice of listing bioequivalence data requirements for a listed drug at the time a pharmaceutically equivalent drug is approved.<sup>281</sup>

In addition, your interpretation would render several other provisions of section 505(j) superfluous.<sup>282</sup> For example, section 505(j)(3)(b) requires the Agency to meet with an ANDA applicant to agree on the design and size of bioequivalence studies needed for approval if an applicant submits a reasonable written request for such a meeting. Under your view, the bioequivalence method would had to have been determined and published when FDA first approves and lists the RLD, and there would be no reason for such meetings with the ANDA applicant.

As a practical matter, your view would require the Agency to expend enormous resources to generate and evaluate the scientific data required to establish bioequivalence requirements, data the FD&C Act requires ANDA holders to provide in the ANDA.<sup>283</sup> There is no evidence that Congress intended to place such a burden on the Agency through subsection 505(j)(a)(7)(A).<sup>284</sup>

#### 8. Your Requests for an Opportunity to Comment on the Bioequivalence Recommendation for Generic Vancomycin Capsules Have Been Satisfied

In multiple submissions you have requested that FDA (1) publish and provide opportunity for public comment on FDA's vancomycin bioequivalence recommendation;<sup>285</sup> (2) provide the scientific rationale underlying any bioequivalence recommendation;<sup>286</sup> (3) refrain from approving any ANDA prior to publication of such

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particular approved product as therapeutically equivalent to other pharmaceutically equivalent products (first letter) and to provide additional information on the basis of FDA's evaluations (second letter)." *Id.* at xiii. This additional information indicates the bioequivalence methodology utilized by the sponsor of the product. *Id.* at xv.

<sup>280</sup> VP Dec. 22, 2010, Supp. at 1-2.

<sup>281</sup> See, e.g., *Schering Corp. v. FDA*, 51 F.3d at 398 (citing section 505(j)(7)(A)(i)(III) as evidence of Congressional intent to provide FDA discretion to determine appropriate bioequivalence methodology through the ANDA approval process).

<sup>282</sup> *Duncan v. Walker*, 533 U.S. 167, 174 (2001) ("It is our duty to give effect, if possible, to every clause and word of a statute. . . . We are thus reluctant to treat statutory terms as surplusage in any setting") (internal citation and quotation omitted).

<sup>283</sup> 21 U.S.C. 355(j)(2)(A)(iv).

<sup>284</sup> *Buckman Co. v. Plaintiffs' Legal Committee*, 531 U.S. 341, 351 and n.6 (2001) (uncontemplated increase of FDA's administrative burden in reviewing regulated products is improper).

<sup>285</sup> See, e.g., Letter fr. T. Doyle, ViroPharma, to H. Winkle, Dir. CDER Office of Pharm. Sci., at 2 (Jan. 30, 2008).

<sup>286</sup> See, e.g., VP Dec. 30, 2007, Letter at 10.

recommendation;<sup>287</sup> and (4) seek expert opinion regarding vancomycin bioequivalence.<sup>288</sup> FDA published the Vancomycin BE Draft Guidance for public comment in 2008, which, as described above, included the Agency's scientific rationale for permitting in vitro dissolution to demonstrate bioequivalence for vancomycin capsules.<sup>289</sup> FDA convened the August 2009 ACPS meeting for the express purpose of gathering expert opinion on the proposed bioequivalence standard for generic vancomycin capsules in a public forum,<sup>290</sup> at which the Agency's scientific rationale for the vancomycin bioequivalence methodology set out in the draft guidance was discussed in great detail.<sup>291</sup> Both of these events occurred prior to the approval of any vancomycin capsule ANDA. Your requests outlined above therefore have largely been satisfied. To the extent that the particular bases on which you requested these actions require additional discussion, we address those issues below.

(a) FDA Appropriately Distributed Bioequivalence Recommendations

You claim in your initial submissions that the 2006 Revised Recommendation should be rescinded because the "letter" method of distributing bioequivalence standards violated several statutes or policies including the *Freedom of Information Act*, the *Data Quality Act*,<sup>292</sup> FDA good guidance practices,<sup>293</sup> FDA's Standards of Conduct,<sup>294</sup> and FDA's historical controlled correspondence procedures.<sup>295</sup> FDA concludes that these arguments are moot because the Agency has since issued guidance outlining the recommended bioequivalence methodology for vancomycin. In addition, FDA no longer uses the letter method as the primary means of publicly distributing bioequivalence recommendations.<sup>296</sup> As described above, FDA consistently has issued product-specific recommendations through Specific Product BE Guidance process since 2007,<sup>297</sup> and there is no reasonable expectation that FDA will cease this practice and return to a letter-only method of distributing bioequivalence recommendations in the future.<sup>298</sup>

You make a related claim that you were caught "unawares" when one party released the contents of its 2006 letter indicating that FDA may accept in vitro dissolution data, and

<sup>287</sup> Id. at 11.

<sup>288</sup> VP Draft Guidance Resp. at 39.

<sup>289</sup> Draft guidance for industry on *Bioequivalence Recommendation for Vancomycin HCl*; Availability, 73 FR 76362 (Dec. 16, 2008).

<sup>290</sup> *Advisory Committee for Pharmaceutical Science and Clinical Pharmacology*; Notice of Meeting, 74 FR 26249 (June 1, 2009).

<sup>291</sup> 2009 ACPS Tr. at 35-90, 294-328.

<sup>292</sup> (Pub. L. No. 106-554, 114 Stat. 2763 (2000) section 515 Appx. C).

<sup>293</sup> Section 701(h) of the FD&C Act.

<sup>294</sup> 21 CFR part 19.

<sup>295</sup> VP May 31, 2006, Supp. at 7-14; VP Jan. 15, 2010, Supp. at 19-27.

<sup>296</sup> Specific Product BE Guidance at 2-3. To note, FDA does provide bioequivalence recommendations by letter to members of the public who request such information for products for which specific product guidances are not yet available or for which final guidances have not been completed.

<sup>297</sup> See <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>, last accessed on January 30, 2012 (listing 946 product-specific bioequivalence recommendations issued).

<sup>298</sup> *Larsen v. U.S. Navy*, 525 F.3d 1, 4 (D.C. Cir. 2008) (claims moot when "there is no reasonable expectation ... that the alleged violations will recur") (internal quotation omitted).

that FDA acted in violation of the Administrative Procedure Act by allegedly treating similarly situated parties differently by distributing this information only to specific parties, failing to provide a rationale for the Agency's decision, and for selectively disclosing information.<sup>299</sup> As was customary at that time, FDA sent the 2006 Revised Recommendation for vancomycin to each party that had requested such information. Had ViroPharma requested that information, as numerous other entities (including multiple drug manufacturers) did, ViroPharma would have received the same information.<sup>300</sup>

To the extent that your challenge to the letter method is based on your desire for an opportunity to comment on any bioequivalence recommendation for generic vancomycin, you have been given extensive opportunity to advocate for your position on past and current recommended standards prior to the approval of any generic vancomycin product, through the advisory committee process, the draft guidance process, and this citizen petition process. Therefore, any notice-related concerns stemming from FDA's use of the letter method in 2006 have been adequately addressed.<sup>301</sup>

(b) FDA Is Not Required to Provide Notice and Opportunity for Comment Prior to Amending a Recommendation for a Specific Drug Product

You contend that FDA must engage in notice-and-comment rulemaking prior to changing a bioequivalence recommendation for a specific generic drug product.<sup>302</sup> In support of your position, you cite the *Alaska Hunters* line of authority, under which the D.C. Circuit has held that “[w]hen an agency has given its regulations a definitive interpretation, and later significantly revises that interpretation, the agency in effect has amended its rule, something it may not accomplish without notice and comment rulemaking.”<sup>303</sup> Your reliance on this precedent is misplaced.

*Alaska Hunters* requires that the contested agency decision be a “definitive interpretation” of a regulation to be subject to the notice-and-comment rulemaking

<sup>299</sup> VP May 24, 2006, Supp. at 13 (citing 5 U.S.C. 706(2)(a)).

<sup>300</sup> You also attempt to impugn FDA by referencing the fact that FDA did not send letters to these entities directly in the order in which the Agency received requests for information, and that different individuals signed several of the letters (VP May 21, 2006, Supp. at 13; VP Dec. 2, 2009, Supp. at 22-26). You do not assert, however, that FDA failed to provide the information to entities that had requested it, or that FDA intended to provide advantage to or impair any of those entities by accelerating or delaying a letter. Nor do you assert that any of the signatories lacked the authority to sign the letters. Notably, as evidenced in several of your numerous charts detailing when FDA received and sent correspondence (VP Dec. 2, 2009, Supp. at 22-26), FDA responded to all pre-existing requests for information within one month of the March 6 letter you reference. Although the process by which FDA disseminated the letters was not a precise “first-in first-out” process, nothing in your detailed examination of the postmark dates evidences bad faith or negligence on FDA's part.

<sup>301</sup> *Novartis v. Leavitt*, 435 F.3d 344, 349 (D.C. Cir. 2006) (no notice and comment required when drug manufacturer otherwise received opportunity to comment on dosage form designation).

<sup>302</sup> VP May 31, 2006, Supp. at 8, 22; VP May 17, 2007, Supp. at 9, 12; VP Dec. 30, 2007, Supp. at 10-11; VP Dec. 2, 2009, Supp. at 4.

<sup>303</sup> *Alaska Professional Hunters Assoc. v. FAA*, 177 F.3d 1030, 1034 (D.C. Cir. 1999).

requirement.<sup>304</sup> By their very nature, recommended bioequivalence standards are not “definitive interpretations” of the bioequivalence regulations. Instead, they are *recommendations* and do not preclude an applicant from pursuing an alternative method under section 320.24. Indeed, the Draft Vancomycin BE Guidance expressly states that the proposed methods “represent the Agency’s current thinking on a topic and should be viewed only as recommendations.”<sup>305</sup> They are nonbinding and “do not establish legally enforceable responsibilities.”<sup>306</sup> FDA therefore is not required to employ notice-and-comment rulemaking to amend a bioequivalence recommendation for a specific drug product.<sup>307</sup>

(c) The Agency Is Not Required to Provide Notice and Opportunity for Comment on a Bioequivalence Recommendation Before Approving an ANDA That Applies the Recommendation

You similarly assert that FDA must provide notice and an opportunity to comment on an amended bioequivalence recommendation (and the administrative record underlying the amended bioequivalence recommendation) prior to approval of a generic product consistent with that amended recommendation.<sup>308</sup> Under your theory, each time FDA allows an ANDA applicant to demonstrate bioequivalence using a new methodology, it changes the Agency’s interpretation of the bioequivalence regulations, and thus, FDA first would be required to conduct notice-and-comment rulemaking. This argument relies upon a misunderstanding of the function of the bioequivalence regulations. They do not set out bioequivalence recommendations for individual products. Rather, the regulations

<sup>304</sup> *Env’tl. Integrity Project v. EPA*, 425 F.3d 992, 998 (D.C. Cir. 2005) (finding improper EPA’s promulgation of final regulations inconsistent with prior Agency decisions and proposed regulations without notice-and-comment rulemaking (NCRM)); *Paralyzed Veterans of Am. v. D.C. Arena L.P.*, 117 F.3d 579, 586 (D.C. Cir. 1997) (requiring NCRM for “fundamental modification of [a] previous interpretation”); *Mercy Medical Skilled Nursing Facility v. Thompson*, No. 01-2014, 2004 U.S. Dist. LEXIS 27365, at \*5 (D.D.C. May 14, 2004) (secretary’s manual violated APA “because it constitutes a change in the Secretary’s definitive interpretation made without [NCRM]”); *Tripoli Rocketry Assn. v. ATF*, 337 F. Supp. 2d 1, 13 (D.D.C. 2004) (Agency reversal of applicability of regulation-based exemption improper without NCRM).

<sup>305</sup> Specific Product BE Guidance at 1; Draft Vancomycin BE Guidance at 1.

<sup>306</sup> Draft Vancomycin BE Guidance at 1. At several points you demonstrate confusion on the term “recommended” as it is used to describe bioequivalence standards for specific drug products, asserting at various times that the recommendations set forth in the Draft Vancomycin BE Guidance serve as FDA’s preliminary *and* final action on the matter of generic vancomycin bioequivalence. VP Mar. 25, 2010, Supp. at 4-6, 24-25. You misconstrue the Agency’s use of the term “recommended” and the nature of the recommended bioequivalence standards. Bioequivalence standards, whether set forth in draft or final guidance, are recommended standards that benefit ANDA applicants by providing guidance on how to develop ANDAs for specific products. They are not requirements, and do not preclude an applicant from using another method of demonstrating bioequivalence so long as the application meets the requirements under the statute, nor do they bind FDA from changing the recommendations on the basis of subsequent scientific or legal developments.

<sup>307</sup> For these reasons, FDA declines to identify all locally acting drug products for which it changed a bioequivalence standard “without public process.” VP Dec. 30, 2007, Supp. at 10.

<sup>308</sup> VP May 31, 2006, Supp. at 22; VP Dec. 30, 2007, Supp. at 10-11; VP Draft Guidance Resp. at 52. You similarly argue that FDA must provide notice and an opportunity to comment on circumstances in which an ANDA applicant may qualify for an exception to the Q1/Q2 sameness requirement for in vitro data (VP Draft Guidance Resp. at 48). For the reasons set forth above, this argument fails as well.

set out procedures for establishing bioequivalence. As detailed above, FDA has followed this regulatory process in accordance with the parameters set out therein, and has determined that in vitro dissolution is the optimal methodology to demonstrate bioequivalence of vancomycin capsules under section 320.24 of the regulations.

Moreover, your argument conflicts directly with two provisions of the FD&C Act. First, FDA cannot delay review or deny approval of an ANDA on the grounds that the Agency has not published and provided a public comment period for a change in a bioequivalence recommendation for a generic product. FDA decides whether to approve an ANDA based on the Agency's evaluation of the scientific information provided in the application, under the requirements of the FD&C Act and regulations, and in reliance upon the Agency's scientific experience and judgment. If the applicant complies with all applicable statutory requirements, the statute directs the Agency to approve the application regardless of whether the Agency has published applicable bioequivalence recommendations.<sup>309</sup> The Agency's delay or denial of an ANDA's approval to provide third parties an opportunity to comment on a related bioequivalence recommendation would be inconsistent with this provision of the FD&C Act.

Second, as discussed in detail above, the FD&C Act expressly grants FDA wide discretion to "establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect." The bioequivalence regulations similarly provide that FDA may employ "any ... approach deemed adequate by [it] to measure bioavailability or bioequivalence."<sup>310</sup> Inserting a notice-and-comment requirement before FDA applies a new bioequivalence methodology to one or more applications would restrict this broad authority. Of the many courts that have recognized FDA's broad discretion to determine bioequivalence standards (see section I.B., above), none has suggested that the Agency must, or even should, employ notice-and-comment rulemaking to establish bioequivalence criteria for any drug product.<sup>311</sup>

Your proposal for notice-and-comment rulemaking not only lacks any legal support; it also would impose practical hurdles on FDA's ability to advance the purposes of the Hatch-Waxman Amendments. Your proposed notice-and-comment procedure would stifle innovation in developing bioequivalence methodologies and would greatly slow the approval process for products that satisfy the statutory requirements for approval. You make a related assertion that FDA's determinations of acceptable bioequivalence methods for certain "other" drug products without opportunity for public comment demonstrated the Agency's widespread "abandonment" of clinical endpoint studies "behind closed doors" in violation of FDA's policy on transparency.<sup>312</sup> As explained above, FDA is not required to provide an opportunity for public notice and comment

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<sup>309</sup> Section 505(j)(4) of the FD&C Act.

<sup>310</sup> 21 CFR 320.24(b).

<sup>311</sup> For these reasons, your argument that FDA should provide public notice of and an opportunity to comment on what type of exceptions to the Q1/Q2 sameness requirements FDA will accept lacks merit (VP Draft Guidance Resp. at 48).

<sup>312</sup> VP Dec. 30, 2007, Supp. at 3, 8.

prior to making bioequivalence determinations for specific drug products.<sup>313</sup> Nonetheless, the Agency has convened multiple advisory committee meetings concerning bioequivalence standards, has developed a public process for providing notice and opportunity to comment on proposed bioequivalence recommendations prior to their final adoption in the Specific Product BE Guidance, and has issued over 946 bioequivalence recommendations through this new process.<sup>314</sup> These actions demonstrate the Agency's commitment to openness and transparency.

(d) FDA Is Restricted From Publicly Disclosing Certain Data in Pending ANDAs

Prior to approving any generic vancomycin capsule product, you request that FDA provide the scientific basis for the draft bioequivalence recommendation for generic vancomycin and the data underlying the recommendation.<sup>315</sup> FDA provided this information in the Draft Vancomycin BE Guidance, in the background materials for the August 2009 ACPS, and in section II.B., above.<sup>316</sup> FDA also provided data underlying the Agency's scientific determinations in these materials and directly to you in response to your FOIA requests. Your requests therefore have been granted in this respect. However, the Agency cannot release any scientific data provided by an individual ANDA applicant prior to approval of the ANDA, because of the statutory and regulatory prohibitions against public disclosure of the existence of an ANDA and/or the data contained therein.<sup>317</sup> To the extent that your request seeks such data, your petition is denied.

9. Vancocin Is Not Eligible for 3-year Exclusivity Under Section 505(j)(5)(F)(iv) of the FD&C Act Because of the Limitation on Such Exclusivity for Certain Antibiotic Products Set Forth in Section 505(v) of the FD&C Act

(a) Approval of ViroPharma's December 2011 Supplemental NDA

On December 14, 2011, FDA approved Supplemental New Drug Application (sNDA) 50-606/S-028 for Vancocin Capsules. This "Prior Approval" Efficacy Supplement<sup>318</sup> sought updates to the prescribing information in Vancocin labeling, supported by your

<sup>313</sup> VP Dec. 30, 2007, Supp. at 3-4; VP April 3, 2009 Supp. at 5.

<sup>314</sup> See note 90, *infra*.

<sup>315</sup> See, e.g. VP Letter to H. Winkle, Director, FDA Office Pharm. Science, at 2 (Jan. 30, 2008).

<sup>316</sup> Draft Vancomycin BE Guidance at 1-3; Briefing Information, ACPS Meeting (Aug. 4, 2009), available at

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/UCM173220.pdf>; Addendum, Background

Information, ACPS Meeting (Aug. 4, 2009), available at

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeForPharmaceuticalScienceandClinicalPharmacology/UCM175010.pdf>.

<sup>317</sup> 21 CFR 314.430(b)-(d)(1). There also are civil and criminal restrictions on the release of trade secret and confidential commercial information (21 U.S.C. 331(j) (prohibiting disclosure of any information acquired constituting a trade secret under the FD&C Act); 18 U.S.C. 1905 (prohibiting Federal employees from disclosing trade secret information procured during course of employment)).

<sup>318</sup> Prior approval efficacy supplements are described in 21 CFR 314.70(d).

submission of two clinical safety and efficacy studies. In addition, the labeling changes in the sNDA brought the Vancocin labeling into compliance with the Physician Labeling Rule (PLR).<sup>319</sup> After your sNDA was approved, you filed a supplement to your petition asserting that as a result of the modified labeling, Vancocin is entitled to 3 years of exclusivity against generic competition under section 505(j)(5)(F)(iv),<sup>320</sup> and that generic products could not be approved with any “carve outs” from the Vancocin labeling because any such omissions would render the generic products “less safe or effective” than Vancocin for the remaining non-protected conditions of use.<sup>321</sup> Upon review of your supplement, the applicable law, and the labeling changes approved in the sNDA, FDA concludes that Vancocin is not eligible for a 3-year exclusivity period due to the limitation on such exclusivity for certain antibiotic products set forth in section 505(v) of the FD&C Act.

#### (b) Relevant Statutory and Regulatory Framework

The availability of a 3-year exclusivity period for supplements to previously approved drug products is described in section 505(j)(5)(F)(iv) of the FD&C Act. It provides that “[i]f a supplement to an application approved under subsection (b) . . . contains reports of new clinical investigations (other than bioavailability studies) essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement, the Secretary may not make the approval of an application submitted under this subsection for a change approved in the supplement effective before the expiration of three years from the date of the approval of the supplement under subsection (b).”<sup>322</sup>

However, as explained further below, section 505(v) of the FD&C Act limits the availability of this exclusivity for certain antibiotic drug products. To understand the relevance of section 505(v) to your exclusivity claim, a brief summary FDA’s regulation of antibiotics is set forth below.

At the time the Hatch-Waxman Amendments were enacted, antibiotics like vancomycin were approved under section 507 of the FD&C Act and were not eligible for the patent certifications and exclusivity protection provided by Hatch-Waxman, which applied only to drugs approved under section 505 of the FD&C Act.<sup>323</sup> In the *Food and Drug Administration Modernization Act of 1997* (the Modernization Act). Congress eliminated the separate approval pathway for antibiotics.<sup>324</sup> Section 125 of the Modernization Act

<sup>319</sup> *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, 71 FR 3922 (Jan. 24, 2006), promulgated in 21 CFR 201.56, 201.57.

<sup>320</sup> The same exclusivity is available to prevent approval of products under section 505(b)(2) in section 505(c)(3)(E)(iv). For purposes of this response, we will refer in this discussion only to the exclusivity provided under section 505(j), but the Agency’s conclusions on this issue are applicable to the exclusivity provided for in both sections 505(j) and 505(c).

<sup>321</sup> VP Dec. 22, 2011, Supp.

<sup>322</sup> Section 505(j)(5)(F)(iv) of the FD&C Act. See also 21 CFR 314.108(b)(5).

<sup>323</sup> *Drug Price Competition and Patent Term Restoration Act of 1984*, 98 Stat. 1585, 1585; see also *Glaxo, Inc. v. Heckler*, 623 F. Supp. 69 (E.D.N.C. 1985). Hatch-Waxman’s patent term extension provisions did apply to antibiotics, allowing patent term extensions for certain patents claiming antibiotic drugs (see 35 U.S.C. 156(f)(4)(B)(1984)).

<sup>324</sup> *Food and Drug Administration Modernization Act of 1997*, Pub. L. 105-115, 111 Stat. 2296.

expressly repealed section 507 of the FD&C Act, and provided that drugs approved under section 507 would thereafter be considered to have been reviewed and approved under section 505.

For the purposes of Hatch-Waxman requirements and protections, the Modernization Act created a clear distinction between antibiotic drugs for which the first application was received after the Modernization Act's effective date of November 21, 1997, and those antibiotic drugs for which the first application was received before this date. The latter are commonly referred to as "Old Antibiotics." Applications for antibiotic drugs for which the first application was received subsequent to the enactment of the Modernization Act were treated as any other 505 drug and, among other things, were subject to Hatch-Waxman provisions (including, among others, patent listing, patent certification, and eligibility for exclusivity). In contrast, section 125(d)(2) of the Modernization Act expressly exempted Old Antibiotics from certain enumerated provisions of section 505, including those related to patent listing, patent certification, and exclusivity.<sup>325</sup> The Agency subsequently determined that the section 125(d)(2) exemption applied to all antibiotic moieties for which applications had been submitted prior to November 21, 1997, including applications that had been withdrawn, refused for filing, or had failed to obtain approval. FDA explicitly identified vancomycin as a moiety in that group.<sup>326</sup>

On October 8, 2008, Congress enacted section 4 of the *QI Program Supplemental Funding Act of 2008* (the QI Act), entitled "Incentives for the Development of, and Access to, Certain Antibiotics."<sup>327</sup> The QI Act incorporated Old Antibiotics into the Hatch-Waxman regulatory scheme for the first time, with certain limitations. Among other things, the QI Act removed the Modernization Act's enumerated exemptions in section 125(d)(2) for Old Antibiotics,<sup>328</sup> and created in section 505(v) a limited opportunity for an application containing an Old Antibiotic to obtain Hatch-Waxman

<sup>325</sup> Section 125(d) of the Modernization Act states:

Exception. – The following subsections of section 505 (21 U.S.C. 355) shall not apply to any application for marketing in which the drug that is the subject of the application contains an antibiotic drug and the antibiotic drug was the subject of any application for marketing received by the Secretary of Health and Human Services under section 507 of such Act (21 U.S.C. 357) before the date of the enactment of this Act: (A)(i) Subsections (c)(2), (d)(6), (e)(4), (j)(2)(A)(vii), (j)(2)(A)(viii), (j)(2)(B), (j)(4)(B), and (j)(4)(D); and (ii) The third and fourth sentences of subsection (b)(1) (regarding the filing and publication of patent information); and (B) Subsections (b)(2)(A), (b)(2)(B), (b)(3), and (c)(3) if the investigations relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted.

<sup>326</sup> *Marketing Exclusivity and Patent Provisions for Certain Antibiotic Drugs; Proposed Rule*, 65 FR 3623, 3627 (January 24, 2000).

<sup>327</sup> *QI Program Supplemental Funding Act of 2008*, Pub. L. No. 110-379, 122 Stat. 4075.

<sup>328</sup> Section 505(v)(4) of the FD&C Act.

exclusivity, if that application (or supplemental application) was submitted after the QI Act's enactment.<sup>329</sup> Specifically, section 505(v)(2)(A) provides that:

Notwithstanding any provision of the Food and Drug Administration Modernization Act of 1997 or any other provision of law, a sponsor of [an Old Antibiotic] shall be eligible for, with respect to the drug, the 3-year exclusivity period referred to under clauses (iii) and (iv) of subsection (c)(3)(E) and under clauses (iii) and (iv) of section (j)(5)(F), subject to the requirements of such clauses, as applicable.<sup>330</sup>

However, this new availability of 3-year exclusivity for Old Antibiotics was not without limitation. Rather than simply placing new applications and supplements for Old Antibiotics under the pre-existing Hatch-Waxman regulatory scheme, Congress prescribed specific limits to this eligibility under section 505(v)(3)(B) of the FD&C Act. The QI Act provides that 3-year exclusivity period is not available for “any condition of use for which the [Old Antibiotic] . . . was approved before the date of the enactment [of the QI Act].”<sup>331</sup>

The QI Act does not expressly define what constitutes a “condition of use . . . approved before the date of enactment.” As an initial matter, FDA concludes that this limitation must exclude from exclusivity some applications and supplements containing new clinical studies that otherwise would qualify a non-Old Antibiotic product for 3-year Hatch-Waxman exclusivity under 505(j)(5)(F)(iv) (i.e., those “reports of new clinical investigations . . . essential to the approval of the supplement and conducted or sponsored by the person submitting the supplement”). To conclude otherwise would render the limitation in 505(v)(3)(B) meaningless — such a reading would exclude from 3-year Hatch-Waxman exclusivity only those studies that already do not qualify for such exclusivity. Thus, to give content to this limitation, FDA must find that there is a higher hurdle for exclusivity for an Old Antibiotic than there is for another kind of product seeking 3-year exclusivity.<sup>332</sup>

The legislative history of the QI Act indicates that Congress enacted the provision to encourage development of truly novel antibiotics and novel uses of Old Antibiotics, including those that qualified as Old Antibiotics because they had been previously submitted to the Agency, despite the fact that they had never been marketed. Congress sought to balance the need to encourage development of new antibiotic drugs to combat the growing number of disease-resistant bacterial infections and the desire to ensure access to previously approved antibiotics through approval of generic versions of such antibiotics. As described by Senator Burr: “Section 4 [of the QI Act], entitled ‘Incentives

<sup>329</sup> Section 505(v)(1) of the FD&C Act. Congress also included separate exclusivity incentives for Old Antibiotics that had been submitted for review but had not been approved prior to 1997. Section 505(v)(2) of the FD&C Act.

<sup>330</sup> Section 505(v)(2)(A) of the FD&C Act.

<sup>331</sup> Section 505(v)(3)(B) of the FD&C Act.

<sup>332</sup> When Congress includes limiting language in one section of a statute but omits it from another, “it is generally presumed that Congress acts intentionally and purposefully in the disparate inclusion or exclusion.” *Russell v. United States*, 464 U.S. 16, 23 (1983) (internal quotation omitted).

for the Development of and Access to Certain Antibiotics,' is an important step forward to help spur research on new antibiotics and provide incentives for the creation of additional generic antibiotics."<sup>333</sup> By adding new exclusivity provisions, the legislation created incentives for sponsors to find new uses for Old Antibiotics, and bring "old but never approved" antibiotics to the market.<sup>334</sup> By incorporating Old Antibiotics into the Hatch-Waxman patent certification scheme (which allowed, among other things, for challenges to applicable patents pre-approval), the QI Act also facilitated approval and marketing of generic copies of antibiotics approved under section 507.<sup>335</sup>

Upon review of the statute and the available legislative history, FDA interprets 505(v)(3)(B) to permit 3-year Hatch-Waxman exclusivity for Old Antibiotics only for a significant new use for an Old Antibiotic (such as a new indication for a previously approved antibiotic, or a new approval for a submitted but never previously approved antibiotic), not for refinements in labeling related to previously approved uses for Old Antibiotics. This interpretation is consistent with the balance sought by Congress in the QI Act to reward and provide incentives for companies to develop innovative new uses of Old Antibiotics while also facilitating antibiotic access generally through generic approvals and limiting the time period in which the innovator product is the only product on the market.<sup>336</sup>

(c) Vancocin Is Not Eligible for 3-Year Exclusivity Under Section 505(v) of the FD&C Act Because Approval of the December 2011 Supplement Did Not Constitute Approval of a New Condition of Use

Prior to evaluating whether the labeling changes approved in December 2011 meet the requirements for exclusivity set forth in section 505(j)(5)(F)(iv), the Agency must determine whether Vancocin, as an Old Antibiotic, is eligible for the 3-year exclusivity in light of the restrictions of section 505(v) of the FD&C Act. FDA first concludes that Vancocin meets the requirements of section 505(v)(2)(A), in that the sNDA approved in December 2011 was an application for marketing submitted after the enactment of section 505(v), in which the drug that is the subject of the application contains an

<sup>333</sup> 154 Cong. Rec. S 9638, 9638 (Sept. 26, 2008) (statement of Sen. Burr); see also 153 Cong. Rec. S 5624, 5625 (May 7, 2007) (statement of Sen. Hatch when originally proposing bill in 2007) ("[t]he Hatch amendment is intended to be an initial step in the fight against the resistant strains of bacteria by increasing incentives and innovation"); 154 Cong. Rec. H10170, 10171 (Sept. 27, 2008) (statement of Rep. Sullivan) ("[T]his bill provides an important correction in FDA policy regarding the development of antibiotics.").

<sup>334</sup> See 153 Cong. Rec. S. 5624, 5630 (May 7, 2007) (statement of Sen. Kennedy) ("The amendment strikes the right balance between innovation and access, and closes a loophole that eliminated the incentives to bring old but never approved antibiotics to market").

<sup>335</sup> See 154 Cong. Rec. at S 9638 (statement of Senator Burr) (indicating that the Modernization Act "had negatively impacted generic drug companies' ability to obtain approval of and market generic equivalents of antibiotics approved under section 507").

<sup>336</sup> As Senator Kennedy stated in the context of making available to Old Antibiotics the 5-year exclusivity for new chemical entities, "the [Old Antibiotic] amendment would make certain molecules that are part of old active ingredients eligible for recognition as new active ingredients, provided they will be used for a *new indication*. This provision includes limits that would prevent pharmaceutical manufacturers from abusing the process to extend the life of old active ingredient drugs" (153 Cong. Rec. S 5759, 5823 (May 9, 2007) (emphasis added)).

antibiotic drug that was the subject of an application approved by the Secretary under section 507 of the FD&C Act. The question then becomes whether Vancocin is subject to the limitation in section 505(v)(3)(B), which precludes exclusivity if the December 2011 labeling supplement was for approval of labeling changes based on new clinical studies in a “condition of use . . . approved before the date of enactment.”

You contend that Vancocin’s labeling has undergone “fundamental and extensive changes” that constitute “numerous new conditions of use” for Vancocin. Specifically, you contend that the Vancocin labeling changes include the following:

- Inclusion of a clinical studies section supporting one of the already approved indications (CDAD)
- Inclusion of the clinical data in the adverse reactions section related to use in CDAD patients
- A direction for monitoring renal function in CDAD and SAE patients over 65 years of age based on a risk of nephrotoxicity
- An advisory to clinicians to be aware of the importance of appropriate duration of the Vancocin treatment (7-10 days) for geriatric CDAD patients, who may take longer to respond to therapy
- A new indication for use, because the CDAD indication changed from “treatment of antibiotic-associated *pseudomembranous colitis* caused by *C. difficile*” to “treatment of *C. Difficile*-associated diarrhea”
- A new dosing regimen for CDAD patients because the dosage and administration of the 125 mg capsules changed from “500 mg to 2 g administered orally for 7-10 days” to “125 mg orally 4 times a day for 10 days.”<sup>337</sup>

As explained in detail below, FDA concludes that the revision of the Vancocin label to incorporate clinical data that supports and refines labeling regarding already approved conditions of use, does not constitute approval for a condition of use that has not been “approved before the date of enactment” within the meaning of section 505(v)(3)(B). Therefore, these labeling changes do not merit 3-year exclusivity under the limitation on such exclusivity for an Old Antibiotic subject to section 505(v)(3) of the FD&C Act. First, FDA finds that the first four changes cited above relate to and refine the currently approved indication for treatment of CDAD in already identified patient populations, and do not constitute a significant expansion in the conditions of use of the product.

Second, FDA does not find that Vancocin’s modified labeling supports a “changed indication.”<sup>338</sup> “Antibiotic-associated *pseudomembranous colitis* caused by *C. difficile*” and “*C. difficile*-associated diarrhea” are not mutually exclusive definitions. “Pseudomembranous colitis” implies that the diagnosis was made pathologically (through endoscopy) rather than a clinical diagnosis using the toxin assay in stool. Diagnoses are typically made (both in the clinical trials that ViroPharma submitted in support of its labeling sNDA and in general clinical practice) based upon a positive *C. difficile* toxin

<sup>337</sup> VP Dec. 22, 2001, Supp. at 6-7. We note that many of your modifications were required to bring your labeling into compliance with the PLR.

<sup>338</sup> Id. at 7.

assay associated with diarrhea and may not necessarily be associated with the prior use of antibiotics.<sup>339</sup> Thus the labeling changes clarified the previously approved indication but did not constitute a new indication.<sup>340</sup>

Third, FDA rejects your claim that the new labeling included a new dosing regimen. Rather, the dosing regimen you claim is new — “125 mg orally 4 times a day for 10 days” — is encompassed within and is at most a refinement of the prior regimen of “500 mg to 2 g administered orally for 7-10 days.” Nor can you claim that this refinement is an innovation, as “125 mg administered 4 times daily” dose of vancomycin has been adopted as the “standard dose” since the 1980s.<sup>341</sup> Antibiotic guides, such as the *Sanford Guide to Antimicrobial Therapy*, recommend the “125 mg po qid × 10-14 days” regimen (as listed for “*C. difficile* toxin positive antibiotic-associated colitis”).<sup>342</sup>

Notably, ViroPharma’s position that these studies were essential to the approval of a new indication and new dosing regimen are inconsistent with the contents of the sNDA that contained those studies, and the letter detailing the approval of the sNDA. As indicated in the approval letter, the Agency determined that the supplement supported “updates to the prescribing information” and “conversion of the current label into the [PLR] format.”<sup>343</sup> In addition, had you intended to seek approval for a new indication or a new dosing regimen (or a new active ingredient, new dosage form, or new route of administration), you would have been required by statute to have conducted an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients under the *Pediatric Research Equity Act* (PREA).<sup>344</sup> You did not submit any such assessments in your sNDA or otherwise reference PREA’s requirements by seeking a deferral or waiver of this requirement. Moreover, your approval letter, to which you did not object, confirmed that PREA was not triggered by your sNDA. This

<sup>339</sup> Bartlett, J.G., Gerding, G.N., “Clinical Recognition and Diagnosis of *Clostridium difficile* Infection.” *Clin Infect Dis.* 2008; 46 Suppl 1:S12-8. This labeling change also provided for clarity and consistency throughout the label and would have been made along with changes for the Physician’s Labeling Rule conversion without the data from these trials.

<sup>340</sup> Your claim that *staphylococcus aureus* is no longer included as an indication Vancocin’s labeling is unsupported, and contradicted by the Company in its own advertising. Your website states “[o]ur product VANCOCIN® is the only antibiotic approved to treat two significant bacterial infections of the lower digestive tract. The product is . . . indicated for the treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains) and antibiotic-associated pseudomembranous colitis caused by *Clostridium difficile*.” We note that the Vancocin labeling change from “may be administered orally for treatment of enterocolitis caused by . . . [*s. aureus*], to the statement that the drug is “also used for the treatment of enterocolitis caused by [*s. aureus*]” is a minor change in syntax. In addition (a) the sNDA did not include any data or information supporting this change; (b) the use information on [*s. aureus*] (still) appears in the “Indications and Usage” section of the label; and (c) dosing instructions for staphylococcal enterocolitis are provided in the “Dosage and Administration” section of the labeling.

<sup>341</sup> Bartlett, J.G. “The Case for Vancomycin as the Preferred Drug for Treatment of *Clostridium difficile* infection.” *Clin Infect Dis.* 2008; 46: 1489-1492.

<sup>342</sup> Gilbert, D.N., Moellering, R.C., Eliopoulos, G.M., Sande, M.A., “The Sanford Guide to Antimicrobial Therapy,” 38th ed. *Antimicrobial Therapy*; 2008:16.

<sup>343</sup> See letter fr. Katherine A. Laessig, FDA, to ViroPharma, Inc., Approval of sNDA, NDA 50-606/028 (December 14, 2011).

<sup>344</sup> Pub. L. No. 108-155, 117 Stat. 1936 (2003), codified in section 505B(a) of the FD&C Act.

confirms that you, like the Agency, did not believe your labeling changes constituted a new indication, new dosing regimen, or other PREA-triggering change.

The Agency would not discourage any sponsor's effort to modify labeling to provide doctors and patients with current information based on clinical data, and the Agency actively encourages sponsors to bring their labels into compliance with the PLR. Revising the labeling and providing clinical data that supports or, at most, refines information about already approved conditions of use, however, does not give rise to an approval for a condition of use that has not been previously approved and therefore merits the limited 3-year exclusivity available for an Old Antibiotic product. As we have noted previously, the unique history of development of antibiotic regulation reflects Congressional policy judgments that balance the incentives for new antibiotic development and development of new uses for Old Antibiotics against the desire to speed availability of generic antibiotic products in the marketplace.<sup>345</sup> FDA's decision here that Vancocin is not eligible for 3-year exclusivity because of the limitation of section 505(v)(3) is consistent with those policies.<sup>346</sup>

#### 10. Neither ViroPharma Nor Congress is Entitled to Receive Prior Notice of Agency Approval Action

In your December 2011 supplement, you also request that in the event FDA determines it appropriate to approve any generic or 505(b)(2) applications referencing Vancocin prior to December 15, 2014, the Agency provide both you and members of the U.S. Senate Health, Education, Labor, and Pensions (HELP) Committee and the U.S. House of Representatives Energy and Commerce Committee with 30 days notice prior to final approval of any such application.<sup>347</sup> Under applicable statutory and regulatory provisions, FDA generally is prohibited from disclosing any information regarding the filing of an application or approvability of a drug product before the Agency has approved the application, unless its existence has been "previously disclosed or acknowledged."<sup>348</sup> Although the existence of ANDAs for generic vancomycin has been publicly acknowledged, FDA cannot provide you or rank-and-file members of Congress information related to approval of such any application before it is approved. Accordingly, your request for prior notice related to the impending approval of ANDA or 505(b)(2) applications is denied.

<sup>345</sup> Letter to M. Labson, et al., from J. Woodcock re. Docket No. 2009-P-0038 (Mar. 17, 2009).

<sup>346</sup> FDA also notes that even if Vancocin were not subject to the limitation on 3-year exclusivity in 505(v)(3)(B), three-year exclusivity, itself, is not a bar to ANDA approval if the Agency determines that the information protected by that exclusivity can be removed from the ANDA labeling and the ANDA will remain safe and effective for the remaining non-protected conditions of use. See 21 CFR 314.127(a)(7) (providing that FDA will refuse to approve an ANDA that omits labeling protected by exclusivity unless FDA determines that the omission does not render the ANDA less safe or effective for the remaining non-protected conditions of use).

<sup>347</sup> VP Dec. 22, 2011, Supp. at 25.

<sup>348</sup> See 21 CFR 314.430(b).

**D. FDA Developed and Amended the Vancomycin Capsule Bioequivalence Recommendations Through a Lawful and Sound Process**

In addition to your scientific and legal challenges, you assert that the actions of certain FDA employees during the development of the vancomycin capsule bioequivalence recommendation so tainted the process that the current and previous recommendations should be rescinded, and that the Agency should not approve generic vancomycin products using the methodologies set forth in the Draft Vancomycin BE Guidance. FDA takes such assertions very seriously, and has reviewed carefully the issues you have raised. Upon consideration of your filings and of the record you submitted in support of your petition, we conclude that the bioequivalence recommendation for generic vancomycin capsules set forth in the 2008 Draft Vancomycin BE Guidance and in this response has a sound scientific basis. It is the result of thorough Agency review, aided by extensive expert and public consideration and comment.

FDA acknowledges that the process employed in undertaking certain Agency actions, or the Agency's failure to take certain actions, during the course of developing the bioequivalence recommendation for vancomycin was not always optimal. The effect of any early procedural missteps, if any, however, has been remedied by subsequent procedurally and scientifically sound actions. FDA's current bioequivalence methodology recommendations are scientifically sound, and ViroPharma and other interested stakeholders have been given any process that they were due. Moreover, the facts do not support your allegations of wrongdoing by Agency employees. Accordingly, we deny your request that FDA rescind the bioequivalence standard for vancomycin capsules and refrain from approving any ANDAs consistent with the recommendation due to the alleged deficiencies in process.

**1. ViroPharma's Improper Use of the Petition Process and Improper Reference to Predecisional Agency Materials**

We address two preliminary matters before addressing the substance of your process claims. First, FDA notes that you have petitioned FDA in a fashion analogous to interrogatories in civil discovery, demanding answers to more than 170 individual factual questions related to the Agency's development of the vancomycin bioequivalence recommendation.<sup>349</sup> This is an improper use of the citizen petition process. The petition procedure enables parties to "petition the Commissioner to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action."<sup>350</sup> "Administrative action" is defined in relevant part as "every act, including the refusal or failure to act, involved in the administration of any law by the Commissioner."<sup>351</sup> The "action" you request the Agency to take here — to respond directly to factual questions regarding certain Agency decisions — is secondary to your underlying challenge of those decisions. In the interest of a thorough evaluation of the

<sup>349</sup> See, e.g., VP Jan. 15, 2010, Supp. at 5-30.

<sup>350</sup> 21 CFR 10.25(a).

<sup>351</sup> 21 CFR 10.3(a).

many issues you raise, however, FDA has incorporated these questions and the events referenced therein in its consideration of your petition.

Second, you extensively cite FDA employee statements made or actions taken during the consideration of and prior to the Agency's amendment of the vancomycin bioequivalence recommendation in 2006 and 2008, as evidence that FDA, and OGD in particular, believed it lacked scientific and legal authority to recommend in vitro dissolution data, and acted improperly in order to "hide" this deficiency. As explained below, the examples that you cite do not support your claim. Of more fundamental concern, your reliance on FDA employee predecisional statements or actions overlooks a cornerstone principle of the administrative process. As courts have long recognized, Agency employees must enjoy the free exchange of scientific opinions while making a decision, without the threat of public scrutiny of the deliberative process. Perhaps best expressed in the FOIA context, courts consistently warn against the chilling effect of predecision review of scientific determinations, holding that "scientists should be able to withhold nascent thoughts where disclosure would discourage the intellectual risk-taking so essential to technical progress."<sup>352</sup>

Importantly, this policy does not exclude the public from participation in the bioequivalence recommendation development process, nor does it preclude public review and challenge of the Agency's final determinations. Indeed, as illustrated in this instance, FDA has provided extensive notice of and actively has solicited comment on FDA's proposed bioequivalence recommendations before approving any proposed generic vancomycin product and before finalizing the Draft Vancomycin BE Guidance. Rather, the policy "allows agencies a space within which they may deliberate."<sup>353</sup> Your effort to characterize Agency deliberations as duplicitous is unsupported, and provides no basis to rescind Draft Vancomycin BE Guidance or to refrain from approving an ANDA consistent with the recommendation.

## 2. Public Statements Made by FDA Employees Regarding Bioequivalence Recommendations for Generic Vancomycin Capsules Were Not Misleading

You assert that FDA employees publicly misrepresented the Agency's activities in light of FDA's subsequent amendment of the recommendations in 2006 and 2008. These purported misrepresentations, you maintain, evidence a culture of secrecy that taints the Agency's decision-making process.<sup>354</sup> Your principal claim is that OGD's process of developing the vancomycin recommendation was improperly secretive because you were not aware of each deliberative step that the Agency took before it amended the recommendation. As discussed above, Agency employees must enjoy the free exchange of scientific opinions while making a decision without the threat of public scrutiny of the deliberative process. Your characterization of this effort as secretive because you were not a party to internal Agency discussions is misplaced. Upon review of your assertions,

<sup>352</sup> *Chemical Mfg. Assn. v. CPSC*, 600 F. Supp. 114, 118 (D.D.C. 1984).

<sup>353</sup> *Wolfe v. Dep't Health and Human Services*, 839 F.2d 768, 776 (D.C. Cir. 1988).

<sup>354</sup> VP Draft Guidance Resp. at 33-36.

the Agency concludes that there is no evidence that OGD engaged in improper activities to hide from public scrutiny its review of bioequivalence methodologies for generic vancomycin.

(a) FDA Employees Did Not Misrepresent the Status of Generic Vancomycin Bioequivalence Recommendations

You assert that before FDA amended the bioequivalence recommendation in 2006 and 2008, Agency employees made public statements that misrepresented the Agency's intention to amend the bioequivalence recommendation soon thereafter.<sup>355</sup> For example, you cite a statement made by OGD Director of Science, Lawrence Yu, Ph.D., at the October 2004 ACPS meeting, that FDA used a clinical-study approach for demonstrating vancomycin bioequivalence. You then infer that such statements "hid" the fact that the Agency was considering the use of in vitro data.<sup>356</sup> These comments in no way were made in bad faith, or in an attempt to hide the Agency's ongoing review of the bioequivalence methodologies. Rather, these statements reflected FDA's then-current conclusions regarding a method or methods by which an ANDA applicant could establish bioequivalence for generic vancomycin. Nor did such statements convey that FDA considered its pre-2006 or post-2006 recommendation to be the Agency's final conclusion on generic vancomycin bioequivalence on which you could justifiably rely. On the contrary, the Agency expressly indicated that such bioequivalence standards continued to be evaluated. The very topic of the 2004 ACPS meeting was the ongoing development of appropriate standards for demonstrating bioequivalence for locally acting drug products.<sup>357</sup> Immediately after the statement you cite, Dr. Yu told the Committee, "[w]hat we want is [...] to develop a scientific basis for the choice of [bioequivalence method], [for] which we need your input on [the] role of pharmacokinetic studies, [the] role for in vitro dissolution studies, [the] role of the clinical studies."<sup>358</sup> In fact, the Agency noted in several of the bioequivalence letters distributed to parties that had requested the information,<sup>359</sup> and after the 2006 change in the recommendation in responses made to Congressional inquiries made on your behalf,<sup>360</sup> that the proposed methods were subject to change as a result of your citizen petition.

<sup>355</sup> VP May 31, 2006, Supp. at 3-6; VP Draft Guidance Resp. at 33-34.

<sup>356</sup> VP May 31, 2006, Supp. at 4 (citing 2004 ACPS Tr. at 274-75). You similarly cite to statements made by FDA representatives between February 2006 and the December 2008 publication of the Vancomycin BE Draft Guidance that referenced the 2006 Revised Recommendation. VP Draft Guidance Resp. at 33-34.

<sup>357</sup> 2004 ACPS Tr. at 273.

<sup>358</sup> Id. at 275.

<sup>359</sup> See, e.g., Letter fr. G. Buehler, OGD Director to [redacted] (Jan. 9, 2004), attached as Ex. 5, VP Mar. 25, 2010, Supp. (in letter setting forth the pre-2006 recommendation for in vivo clinical endpoint studies noting that if an in vitro method "is adequately developed in the future, the FDA might consider comparative in vivo bioassays that correlate with clinical activity as evidence to establish bioequivalence); Letter from D. Conner, Director, OGD Div. of Bioequivalence to [redacted], at 1 (Nov. 1, 2006), attached as Exh. 15 to VP Mar. 25, 2010, Supp. (in letter setting forth 2006 bioequivalence recommendation, "our advice is preliminary. A citizen petition Docket No. 2006P-0124 was submitted to the Agency on March 17, 2006. The response to the citizen petition may result in a revision to the recommendations").

<sup>360</sup> Letter fr. S. Mason, FDA Acting Asst. Commissioner for Legislation to the Hon. A. Specter, at 2 (Oct. 19, 2007) (referencing the citizen petition docket and FDA's ongoing consideration of the bioequivalence recommendation for generic vancomycin).

Even if these employee statements somehow misrepresented the status of the bioequivalence recommendations, which they did not, your attempt to impugn the Agency's decision-making process on the basis of these statements is misplaced. FDA regulations make clear that views of individual FDA staff expressed at meetings or otherwise, do not constitute a final or official administrative action or position.<sup>361</sup> Courts have rejected efforts to cite statements made by FDA employees regarding bioequivalence to demonstrate the Agency's official position on the issue. In *Serono Labs., Inc. v. Shalala*, the D.C. Circuit expressly rejected a party's efforts to cite individual employee statements that revealed pre-decisional disagreement among FDA chemists as evidence that the final Agency action was infirm.<sup>362</sup>

(b) OGD Employee Statements Regarding General Bioequivalence Principles or Other Drug Products Were Not Misrepresentations

You next claim that OGD employees made statements about bioequivalence in general that misrepresented the Agency's activities related to generic vancomycin. For example, you cite a statement made in February 2006 by then-OGD Director Dr. Gary Buehler at the annual meeting of the Generic Pharmaceutical Association that bioequivalence of locally acting drug products was "an ongoing topic of research" at FDA. You contend that this statement was a misrepresentation because FDA disseminated the 2006 Revised Recommendation shortly thereafter.<sup>363</sup> But Dr. Buehler's statement was and remains true: bioequivalence of locally acting drug products was at the time, and continues to be, an ongoing topic of research at FDA. Nothing in this statement can be construed to indicate that FDA would not issue an amended bioequivalence recommendation for generic vancomycin when the Agency determined that it was scientifically appropriate to do so.

You similarly cite a 2005 statement by OGD's Director of the Division of Bioequivalence I, Dale Conner. You quote Dr. Conner as stating that "[b]ioequivalence study designs with clinical endpoints are used for some oral drug products that are not systemically absorbed, such as sucralfate tablets" and that "[w]ith suitable justification, bioavailability and bioequivalence may be established by in vitro studies alone," including some locally acting products."<sup>364</sup> You state that "Dr. Conner offered only one

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<sup>361</sup> 21 CFR 10.65(a) ("[a]ction on meetings and correspondence does not constitute final administrative action subject to judicial review"); 21 CFR 10.85(k) ("A statement or advice given by an FDA employee orally, or given in writing but not under this section [pertaining to advisory opinions] or 10.90, is an informal communication that represents the best judgment of that employee at that time but does not constitute an advisory opinion, does not necessarily represent the formal position of FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.").

<sup>362</sup> *Serono Labs., Inc. v. Shalala*, 158 F.3d at 1321 (rejecting reference to documents that revealed pre-decisional disagreement among FDA chemists as to whether an active ingredient in an ANDA product was the same in RLD); *Fisons Corp. v. Shalala*, 860 F. Supp. at 867-68 (rejecting citation to prior public statements made by Agency employees about how generic impurities would be considered in an ANDA review as evidence of an Agency policy or practice of waiving a bioequivalence requirement, citing subsections 10.65(a) and 10.85(k)).

<sup>363</sup> VP May 31, 2006, Supp. at 4-5.

<sup>364</sup> *Id.* at 4.

example of a locally acting drug suitable for such an in vitro waiver; cholestyramine resins.”<sup>365</sup> You assert that Dr. Conner’s statement and reference to cholestyramine resins implicitly conveyed the Agency’s position that in vitro data would not be sufficient to demonstrate bioequivalence for any other locally product such as generic vancomycin.<sup>366</sup> However, nothing in Dr. Conner’s statement expressed or even implied that cholestyramine resins are the only locally acting product for which in vitro data would be sufficient. This is not a reasonable conclusion to draw from the cited statement.<sup>367</sup>

(c) FDA Employees Do Not Have a Duty to Inform the Public That the Agency Is Considering a Scientific Matter

You next address instances when FDA employees have “not” spoken. For instance, you reference a January 2008 meeting between the Agency and ViroPharma at which, you assert, Dr. Yu indicated that OGD’s 2006 recommendation was based on sound science. You claim this was a misrepresentation because Dr. Yu must have known, but did not share, FDA’s conclusion that vancomycin was not rapidly dissolving in light of the DPQR 2008 Dissolution Study that was issued the following month.<sup>368</sup> You assume that Dr. Yu both knew of and had a duty to disclose the details of the DPQR study before the study was finalized and before FDA considered any results. Again, this conclusion is unsupported, and, as discussed above, fails to recognize the important policy protecting the free exchange of scientific ideas during the decision-making process.

You also assert that FDA representatives should have responded to generic manufacturer Akorn Incorporated (Akorn)’s representation at the July 2008 ACPS that it had data demonstrating vancomycin was rapidly dissolving. You allege that FDA should have disclosed the conclusions of the DPQR 2008 Dissolution Study at the time Akorn presented its data, and that FDA’s failure to do so conveyed to the committee the Agency’s implicit endorsement of Akorn’s presentation.<sup>369</sup> Your argument is misplaced for several reasons. Under the FD&C Act and FDA regulations, the Agency generally is

<sup>365</sup> Id.

<sup>366</sup> VP May 17, 2007, Supp. at 3-4. See also VP Dec. 30, 2007, Supp. at 5 (asserting that the exclusion of a drug product from general summary presentations about bioequivalence indicates FDA’s recognition of its error in approving generics of the unmentioned drug product). You similarly claim that an informational poster presented at a November 2006 meeting was intentionally misleading because it referenced the bioavailability of BCS Class 1 products together with other generic products but did not expressly indicate that a majority of the products reviewed were not BCS-characterized products. Such a presentation by no means indicates, as you assert, that “OGD was more interested in promoting public acceptance of the ‘sameness’ of generic drugs and OGD’s own ability to regulate them than portraying accurately the results of its research” (VP Dec. 30, 2007, Supp. at 6).

<sup>367</sup> You also cite as indicative of OGD’s “penchant for revisionist history” an article by Dr. Gary Buehler regarding the development of bioequivalence review since 1974 (VP Mar. 25, 2010, Supp. at 8-12). This mischaracterization of Dr. Buehler’s article is neither accurate nor productive, and your discussion fails to recognize that FDA’s approach to bioequivalence has evolved against a backdrop of scientific and regulatory developments. Dr. Buehler did not, as you imply, mischaracterize the history of FDA’s consideration of bioequivalence in order to support the use of in vitro data to demonstrate bioequivalence.

<sup>368</sup> VP Draft Guidance Resp. at 32-33.

<sup>369</sup> VP Draft Guidance Resp. at 18, 25.

prohibited from disclosing any determinations regarding the filing or approvability of any pending ANDA for a generic drug product before it has reached a final decision on whether to approve or not approve the application.<sup>370</sup> For FDA to have responded to Akorn's data in the manner you propose would have been in violation of these restrictions. Such a response also would have undermined the purpose of an advisory committee meeting, which is to foster open comment from interested parties.<sup>371</sup> Reflecting this purpose, FDA regulations prohibit non-committee members from responding to other presentations.<sup>372</sup> Your related assertion that in response to Akorn's presentation, Dr. Yu should have informed the committee that FDA was drafting a guidance for vancomycin bioequivalence and that ViroPharma had made certain arguments regarding absorption in patients to the Agency, lacks merit for similar reasons.<sup>373</sup>

### 3. FDA Properly Developed the Generic Vancomycin Bioequivalence Recommendation

#### (a) FDA Properly Developed the 2006 Generic Vancomycin Bioequivalence Recommendation

You argue that the internal process by which FDA developed the 2006 Revised Recommendation was unsound. Specifically, you claim that Dr. Yu unilaterally made the decision in 2006 to permit in vitro dissolution data to demonstrate bioequivalence for generic vancomycin in violation of OGD procedures in an effort to shield from review "his" conclusion to permit in vitro data.<sup>374</sup> This claim is based on a statement Dr. Yu made in a 2009 e-mail in which he said that he made the decision in 2006 to permit in vitro data and others "went along."<sup>375</sup> Notwithstanding this e-mail exchange, it is clear from the Agency documents you have included in support of your petition, that FDA conducted a thorough review in 2006 involving numerous members of the Agency.<sup>376</sup> For example, the internal bioequivalence review memorandum endorsing the 2006 amendment that you cite was signed by two OGD scientists and three OGD managers including the Director of the Division of Bioequivalence, the OGD Associate Director of Medical Affairs, and OGD's Director of Science.<sup>377</sup> You also assert that certain OGD

<sup>370</sup> 21 CFR 314.430(d)(1).

<sup>371</sup> As the committee chair stated at this meeting prior to the public comment period, "[t]he FDA and this Committee place great importance on the open public hearing process. The insights and comments provided can help the Agency and this Committee in their consideration of the issues before them. That said, in many instances, and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by the chair." 2008 ACPS Tr. at 91.

<sup>372</sup> 21 CFR 14.29(f).

<sup>373</sup> VP Draft Guidance Resp. at 25.

<sup>374</sup> VP Dec. 2, 2009, Supp. at 3.

<sup>375</sup> VP Dec. 2, 2009, Supp. at 3 (quoting Aug. 6, 2009, e-mail from L. Yu to C. Parise, D. Nguyen) (attached as Ex. C to supplement).

<sup>376</sup> VP Jan. 15, 2010, Supp., Ex. 15; see also VP Jan. 15, 2010, Supp., Ex. 11 (exhibits include multiple e-mails among many members of OGD confirming concurrence with the vancomycin recommendation).

<sup>377</sup> VP Jan. 15, 2010, Supp., Ex. 15.

employees improperly excluded Dr. Hixon, then Associate Director of Medical Affairs, from the review process.<sup>378</sup> This is unfounded: the documents on which you rely show that Dr. Hixon was involved in the review process and approved the recommendation.<sup>379</sup>

You next contend that the 2006 recommendation was not finalized prior to its release, citing two signed versions of the OGD vancomycin bioequivalence review memorandum with different dates.<sup>380</sup> You are correct that FDA modified its internal bioequivalence review memorandum after the Agency sent several letters setting forth the *in vitro* recommendation. Although this process was imperfect, these modifications were editorial in nature and did not alter the substantive bioequivalence recommendation, or the bases on which OGD rested its recommendation. For example, in the first February 8, 2006, version, the information in the “Formulation” section of the memo is set forth in paragraph form. The same information is set forth in a table format in the February 24, 2006, version. Nothing substantive in the documents changed, and the same individuals signed off on both versions.<sup>381</sup> You also question the sign-off process for the February 8, 2006, memorandum due to the fact that each individual signed the first memorandum on the same day.<sup>382</sup> There is no basis to infer wrongdoing on this ground, and FDA declines your request that the Agency review employee records to determine where each signatory was on February 8, 2006.

Finally, you assert that FDA erroneously relied on data submitted by an ANDA applicant in concluding that vancomycin is rapidly dissolving as defined in the BCS Guidance thereby justifying the use of *in vitro* dissolution data.<sup>383</sup> In response to this concern, which you first voiced in March 2006, FDA conducted its own dissolution study, the findings of which were memorialized in the 2008 DPQR Dissolution Study report discussed above and confirmed in the 2009 DPQR Dissolution Study.<sup>384</sup> Both these studies demonstrated that vancomycin capsules are not rapidly dissolving under the BCS Guidance definition. The 2006 citation to the BCS Guidance therefore was inaccurate. As explained above, however, the BCS Guidance does not describe the only instances in which FDA may consider *in vitro* dissolution data in evaluating bioequivalence. More notably, FDA acknowledged this error, conducted its own *in vitro* dissolution data studies to investigate the claim, reexamined and refined the bioequivalence recommendation, and solicited the expert ACPS’s opinion, which unanimously endorsed use of *in vitro* data notwithstanding the fact that vancomycin does not fall within the BCS Guidance criteria.

<sup>378</sup> VP Jan. 15, 2010, Supp. at 7-9, 11-12.

<sup>379</sup> See, e.g., VP Jan. 15, 2010, Supp., Ex. 11 (exhibit includes multiple e-mails to and from D. Hixon regarding “vancomycin recommendation,” including Jan. 20, 2006, e-mail fr. L. Lee to D. Hixon stating that “we have about 10 controlled correspondences for this drug and would like to know what you think about the recommendation”); Ex. 15 (OGD bioequivalence review memorandum signed by D. Hixon as concurring).

<sup>380</sup> VP Jan. 15, 2010, Supp. at 8-9, 20.

<sup>381</sup> Compare VP Dec. 15, 2009, Supp., Ex. 15 at 8 (Bioequivalence Review for Generic Vancomycin (Feb. 8, 2006)) with Ex. 21 (Bioequivalence Review for Generic Vancomycin at 8 (Feb. 24, 2006)).

<sup>382</sup> VP Jan. 15, 2010, Supp. at 8-9, 20.

<sup>383</sup> VP June 3, 2006, Supp. at 36-37; VP April 3, 2009, Supp. at 2-3.

<sup>384</sup> DPQR 2008 Dissolution Study; DPQR 2009 Dissolution Study.

Thus, any impact of the Agency reliance on inaccurate data in establishing the 2006 recommendation has been mitigated.

(b) FDA Properly Developed the 2008 Amendment to the Generic Vancomycin Bioequivalence Recommendation

You also challenge several aspects of the process by which FDA developed and made public the 2008 amendment to the vancomycin bioequivalence recommendation. You make the unsupported assertion, based on the Agency's October 2008 response to an inquiry from the Alliance for Aging Research (Alliance), that FDA relied on a generic applicant's (Akorn's) faulty data in developing the bioequivalence methodologies that are recommended in the Draft Vancomycin BE Guidance.<sup>385</sup> In July 2008, Alliance asked FDA to make available data correlating in vitro testing with in vivo clinical results for use of vancomycin in CDAD patients.<sup>386</sup> In its response to Alliance in October 2008, FDA explained that it did not have such correlating data, but that in vitro data presented in the July 2008 ACPS meeting by generic manufacturer Akorn related to the dissolution of vancomycin "was consistent with" the Agency's draft bioequivalence recommendation.<sup>387</sup> FDA's letter to Alliance was not accurate because FDA did not rely on Akorn's data. As explained above, the Agency relied on the results of its Internal DPQR 2008 Dissolution Study<sup>388</sup> in formulating the Draft Vancomycin BE Guidance, which results FDA confirmed in the second internal dissolution test in 2009.<sup>389</sup> In addition, FDA mistakenly disclosed in the October 2008 letter to Alliance, the fact that the Agency anticipated issuing the Draft Vancomycin BE Guidance in December of that year. Nonetheless, there is no indication that you or any other party was harmed by this inadvertent disclosure of the impending draft guidance.

You also assert that FDA selectively disclosed the substance of the December 2008 recommendation to Akorn prior to publishing the notice of availability of the Draft Vancomycin BE Guidance in the *Federal Register*, based on the fact that the company referenced comparable dissolution profiles and Q1/Q2 sameness in its presentation at the 2008 ACPS meeting on bioequivalence of low-solubility drug products.<sup>390</sup> This allegation is unfounded. FDA did not "tip off" Akorn as to the draft guidance standard. FDA's thinking on Q1/Q2 sameness previously had been published in policy documents related to other locally acting products. For example, in FDA's May 2008 citizen petition response concerning Acarbose Capsules, another locally acting oral GI drug product, the Agency endorsed the use of in vitro dissolution data to demonstrate bioequivalence for that product, and included a recommendation for Q1/Q2 sameness of inactive ingredients.<sup>391</sup> Q1/Q2 sameness also has been used by the Agency for some time in

<sup>385</sup> VP April 3, 2009, Supp. at 1-3; VP June 25, 2010, Supp. at 11.

<sup>386</sup> Letter to FDA fr. D. Perry, Exec. Dir., Alliance for Aging (Aug. 28, 2008).

<sup>387</sup> Letter fr. FDA to D. Perry, Exec. Dir., Alliance for Aging, at 2 (Oct. 24, 2008).

<sup>388</sup> Draft Vancomycin BE Guidance at 2 (referencing 2008 FDA dissolution study in scientific rationale for draft recommended standard).

<sup>389</sup> DPQR 2009 Dissolution Study.

<sup>390</sup> VP Draft Guidance Resp. at 34; VP Dec. 2, 2009, Supp. at 4; VP Mar. 25, 2010, Supp. at 18-22.

<sup>391</sup> Letter fr. FDA to W. Rakoczy re. bioequivalence of generic acarbose products (May 7, 2008), at 7.

bioequivalence analyses for other locally acting drug products.<sup>392</sup> Your related charge that FDA selectively disclosed the 2008 recommendation to Akorn in order to “enlist” the company to “cultivate an appearance of independent validation” of FDA’s revised standard is similarly unfounded.<sup>393</sup>

Shortly after FDA published the notice of availability for the Draft Vancomycin BE Guidance in the *Federal Register*, the Agency made public a version of the Draft Vancomycin BE Guidance containing certain revised citations in the footnotes to the scientific literature supporting the bioequivalence recommendation.<sup>394</sup> FDA posted the revised version on its Web site consistent with the processes described in the Specific Product BE Guidance<sup>395</sup> and on the Agency’s Guidance Web page.<sup>396</sup> FDA did not reissue notice of the revisions in the *Federal Register*, although it is clear from the Agency documents you cite that FDA employees attempted in good faith to make the revised guidance public.<sup>397</sup> This clearly was not, as you contend, an effort by one FDA employee to circumvent Agency process<sup>398</sup> or evidence of the Agency’s “equivocation on the parameters of the dissolution requirements” or “penchant for behind-closed-door behavior.”<sup>399</sup> Moreover, any prejudice to you that may have resulted from the failure to post a new notice of availability when the amended version of the guidance was published has been mitigated.<sup>400</sup> You were aware of the new version several weeks before you filed your first comments to the Draft Vancomycin BE Guidance in March 2009 (for which FDA granted an extension), and you since have taken multiple opportunities to opine on the contents of the revised draft.<sup>401</sup>

<sup>392</sup> See, e.g. the guidance for industry on *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*, at 8 (April 2003).

<sup>393</sup> VP Mar. 25, 2010, Supp. at 20. Nor has FDA disclosed any protected information to any ANDA applicant regarding inactive ingredients in Vancocin. VP Mar. 25, 2010, Supp. at 30.

<sup>394</sup> Compare Draft Vancomycin BE Guidance at 2, n.2-5, with VP Feb. 27, 2009, Supp., Attachment, Draft Guidance on Vancomycin Hydrochloride, at 2, n.2-5.

<sup>395</sup> Specific Product BE Guidance at 1, n.2 (“[FDA] update[s] guidance documents periodically. To make sure you have the most recent version of product-specific bioequivalence study guidance, check the FDA Drugs guidance page”).

<sup>396</sup> FDA drug guidance documents, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. (“**Note: Draft guidances** are undergoing finalization. Please contact the relevant division for the most up-to-date Agency perspective on an issue.”) (emphasis in original).

<sup>397</sup> See VP Dec. 2, 2009, Supp., Exs. J (E-mail fr. E. Thakur, Program Management Officer, Office of Regulatory Policy, CDER, to M. Bigesby, FDA Legal Instruments Examiner, Division of Dockets Management re. “IMPORTANT changes needed to Posted Vanco Guidance” (Dec. 16, 2009) (“[t]he correct version [of the draft guidance] did not get posted ... It needs to be replaced on the web AS SOON AS POSSIBLE. ... Can this one be replaced quickly, also in FDMS and the docket? ... Please let me know if this needs to be sent to anyone else for these changes to be made.”)). See also VP Dec. 2, 2009, Supp., Exs. K-L.

<sup>398</sup> See VP Dec. 2, 2009, Supp. at 5, and 5 n.17.

<sup>399</sup> VP Draft Guidance Resp. at 31.

<sup>400</sup> *Novartis Pharms. Corp. v. Leavitt*, 435 F.3d at 349 (NDA holder’s request for notice and opportunity to comment in detail on issue moot as innovator already had received “every benefit that it could from a favorable judgment” on the issue).

<sup>401</sup> VP Feb. 27, 2009, Supp. to Vancomycin BE Draft Guidance Docket, at 1-3 (correspondence raising issue regarding Agency failure to republish revised vancomycin draft guidance).

Finally, you assert that FDA improperly made a “post hoc” effort to find legal authority for its decision to permit in vitro dissolution data to establish bioequivalence.<sup>402</sup> In support of this position you cite internal Agency documents that reflect ongoing discussions among OGD staff, FDA attorneys, and senior Agency officials on the appropriate methodology for demonstrating bioequivalence consistent with 21 CFR 320.24. You contend that such discussions demonstrate a “struggle” to find the legal authority to permit FDA to accept in vitro data.<sup>403</sup> You also claim that internal Agency documents that do not mention a specific legal authority demonstrate that FDA did not believe it had the authority to permit in vitro data to demonstrate bioequivalence.<sup>404</sup> Internal Agency discussions of the legal authority and compliance therewith, or the absence of citation to a legal authority in internal documents, do not indicate that FDA thought it lacked authority to take an action. Rather, these documents reflect the Agency’s internal discussion of the legal issues associated with bioequivalence determinations. As courts have concluded, these deliberations of legal and policy issues, like their scientific counterparts are a critical part of the agency’s pre-decision process.<sup>405</sup> As set forth above, FDA has clear legal authority to determine appropriate bioequivalence methodology.<sup>406</sup> Internal discussion (or lack thereof) of FDA’s legal authority by no means limits that authority.

(c) OGD Did Not Misrepresent to Senior FDA Officials the Process by Which the Agency Developed the 2008 Draft Vancomycin BE Guidance

Finally, you assert that OGD misrepresented to senior FDA officials the recommendation development process in order to hide the OGD decision making process from scrutiny.<sup>407</sup> You base this charge largely on briefing materials that appear to have been prepared for internal FDA meetings that you received through FDA’s response to your FOIA request. As a preliminary matter, it is important to recognize that in addition to being pre-decisional, written background materials for oral briefings are summary in nature. They are not comprehensive, nor do they necessarily reflect the discussions that actually took place at any meeting or presentation, or the Agency’s final determination on any given issue. As a result, such materials are limited in their ability to illuminate what senior FDA officials did or did not know about the process by which generic vancomycin bioequivalence recommendations were developed. Notwithstanding these limitations, we address your arguments.

You first contend that OGD did not adequately represent to senior officials the history of the pre-2006 in vivo data requirement. Specifically, you claim that OGD failed to

<sup>402</sup> VP Mar. 25, 2010, Supp. at 23-26; VP Jan. 15, 2010 Supp. at 16-18.

<sup>403</sup> VP Mar. 25, 2010, Supp. at 26.

<sup>404</sup> Id. at 27.

<sup>405</sup> *Wolfe v. Dep’t Health and Human Services*, 839 F.2d at 773 (“As stated in the legislative history, the purpose of [the deliberative process exemption] is to encourage the frank discussion of legal and policy issues”) (internal quotation and citation omitted); *Brinton v. Department of State*, 636 F.2d 600, 604 (D.C. Cir. 1980) (“There can be no doubt that such legal advice, given in the form of intra-agency memoranda prior to any agency decision on the issues involved, fits exactly within the deliberative process rationale.”).

<sup>406</sup> See Section I.B., above.

<sup>407</sup> VP Mar. 25, 2010, Supp. at 16-22.

reference several instances between 1996 and 2006 when FDA communicated to third parties the then-existing recommendation for in vivo studies.<sup>408</sup> As the presentation materials you cite demonstrate, however, OGD accurately represented that it consistently had communicated the in vivo data recommendation up through 2006.<sup>409</sup> These same presentations also reference historical events that led to the 2006 amendment, including the 2004 ACPS discussion on using in vitro dissolution data for locally acting GI products and the 2005 ANDA data submission that purported to demonstrate vancomycin's rapid dissolution rate.<sup>410</sup>

You next assert that a briefing document on generic vancomycin dated April 2009 purportedly presented to then-FDA Deputy Commissioner Joshua Sharfstein was materially inaccurate in several respects with respect to the process by which the Q1/Q2 requirement was developed.<sup>411</sup> The document indicates that OGD had discussed what ultimately became the 2008 amended recommendation (including the Q1/Q2 requirement) in earlier briefings with the relevant review division, the Director for the Center for Drug Evaluation and Research, the Deputy Commissioner and FDA Commissioner. You claim that this statement is inaccurate because there is no reference to Q1/Q2 inactive ingredient sameness in the briefing slides for these earlier meetings. As noted above, such slides are not the entire record of a meeting or presentation, and therefore, do not conclusively establish what actually was discussed at any meeting. In any event, your contention is inaccurate. For example, while "Q1/Q2" may not have been expressly referenced in some of these materials, product formulation, which includes active and inactive ingredients, is referenced.<sup>412</sup>

You also claim that the statement in this briefing document that several ANDAs "would be approvable under the BE in vitro approach" at the time of the briefing could not have been accurate in light of the short time period between announcement of the revised standard (December 2008), which included the Q1/Q2 requirement for the first time, and the briefing (April 2009). You assert that this statement demonstrates that FDA had failed to adequately characterize Vancocin's inactive ingredients prior to permitting in vitro data because if it had, it would have not included the Q1/Q2 requirement due to the complexity of the inactive ingredients in Vancocin.<sup>413</sup> This series of inferences is unsupported.

Even if OGD had misrepresented the history of its development of the bioequivalence recommendation set forth in the Draft Vancomycin BE Guidance to Agency officials -- which it did not -- as detailed in this petition response, the Agency has considered the entire history of the bioequivalence recommendation, and the current scientific bases for

<sup>408</sup> VP Jan. 15, 2010, Supp. at 3-6; VP Mar. 25, 2010, Supp. at 14.

<sup>409</sup> See, e.g., VP Jan. 15, 2010, Supp., Ex. 46, Slide Presentation entitled "Establishing Bioequivalence of Vancomycin HCl Capsules: Commissioner Briefing" (Nov. 8, 2007), FDA-OC-02354-02356.

<sup>410</sup> See id.

<sup>411</sup> VP Jan. Mar. 25, 2010, Supp. at 21; Ex. 53, Memo. re. Vancomycin Bioequivalence Issues, attached to e-mail fr. P. Pilsner to J. Woodcock et al. (April 15, 2009).

<sup>412</sup> Id.

<sup>413</sup> VP Mar. 25, 2010, Supp. at 28-30.

the recommendation, and today endorses the bioequivalence recommendation for generic vancomycin capsules with full knowledge of the process by which it was developed.

### III. CONCLUSION

For the foregoing reasons, FDA has determined that the recommendation in the Draft Vancomycin BE Guidance is scientifically sound, that FDA has clear legal authority to recommend in vitro dissolution data to demonstrate generic vancomycin bioequivalence, and that the process by which the Agency developed the current recommendation involved a robust, public consideration of the issues raised in this petition in accordance with the relevant legal authorities. FDA also has determined that Vancocin is not eligible for a 3-year exclusivity period because of the limitation on such exclusivity set forth in section 505(v) of the FD&C Act.

Sincerely,

A handwritten signature in black ink, appearing to read 'J. Woodcock', is written over the printed name.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research

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# EXHIBIT 4

**REPORT TO CONGRESS**

**FDA Amendments Act of 2007  
Section 914 Public Law 110-85**

**Annual Report on Delays in Approvals of  
Applications Related to Citizen Petitions and  
Petitions for Stay of Agency Action  
For Fiscal Year 2008**

**Department of Health and Human Services  
Food and Drug Administration  
March 2009**

**Submit to HHS for review and concurrence before final signature:**

\_\_\_\_\_  
**Acting Commissioner of Food and Drugs** Date\_\_\_\_\_

## **Statutory Requirement**

On September 27, 2007, the President signed into law the Food and Drug Amendments Act of 2007 (FDAAA) (Public Law 110-85). Section 914 of Title IX of FDAAA took effect on the date of enactment and amended Section 505 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 255) by adding new subsection (q). Section 505 (q) applies to certain petitions that request that FDA take any form of action related to a pending application submitted under Section 505(b)(2) or 505(j) of the Act<sup>1</sup> and governs the manner in which these petitions are treated and states the following:

The Secretary shall annually submit to the Congress a report that specifies—

- (A) the number of applications that were approved during the preceding 12-month period;
- (B) the number of such applications whose effective dates were delayed by petitions referred to in paragraph (1) during such period;
- (C) the number of days by which such applications were so delayed; and
- (D) the number of such petitions that were submitted during such period.

## **I. BACKGROUND**

### **A. Citizen Petitions and Petitions for Stay of Agency Action**

Citizen petitions are a vehicle that stakeholders outside of the Food and Drug Administration (FDA or the agency) can use to ask FDA to take (or refrain from taking) an action. For example, a petitioner can ask the agency to:

- disapprove a drug product application;
- add warnings to a drug's label; and
- change products from prescription to over the counter (OTC) status.

FDA regulations provide the opportunity for any interested person to submit a citizen petition requesting FDA “to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action” (21 CFR 10.25 and 10.30). A petition can also be submitted to stay (delay) the effective date of any administrative action, such as the approval of a certain drug application (21 CFR 10.35). Both citizen petitions and petitions for stay of agency action will be collectively referred to as “petitions” throughout this Report.

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<sup>1</sup> In this report, an application submitted under Section 505(b)(2) of the Act is referred to as a 505(b)(2) application and an application submitted under Section 505(j) of the Act is referred to as an abbreviated new drug application (ANDA)

## **B. Delays of Approvals**

Section 505(q)(1)(A), together with Section 505(q)(5), describes the general scope of Section 505(q). Section 505(q)(1)(A) provides:

The Secretary shall not delay approval of a pending application submitted under subsection (b)(2) of (j) because of any request to take any form of action relating to the application, either before or during consideration of the request, unless-

- (i) the request is in writing and is a petition submitted to the Secretary pursuant to Section 10.30 or 10.35 of title 21, Code of Federal Regulations (or any successor regulations); and
- (ii) the Secretary determines, upon reviewing the petition, that a delay is necessary to protect the public health.

Section 505(q)(1)(A) was recently amended to include the following statement: “Consideration of the petition shall be separate and apart from review and approval of any application.”<sup>2</sup> In Section 505(q)(5), the term *application* is defined as an application submitted under Section 505(b)(2) or 505(j) of the Act and the term *petition* is defined as a request described in 505(q)(1)(A)(i).

If FDA determines, based upon a request for action on a pending application, that a delay of approval of the abbreviated new drug application (ANDA) or 505(b)(2) application is necessary to protect the public health, FDA is required to provide the applicant, not later than 30 days after making the determination, the following information:<sup>3</sup>

- notification that the determination has been made;
- if applicable, any clarification or additional data that the applicant should submit to the petition docket to allow FDA to review the petition promptly; and
- a brief summary of the specific substantive issues raised in the petition which form the basis of the determination.

At FDA’s discretion, the information is to be conveyed by either a document or a meeting with the applicant.<sup>4</sup> The information conveyed as part of the notification is to be considered, part of the application and subject to applicable disclosure requirements.<sup>5</sup>

## **II. STATUTORY REPORTING REQUIREMENT**

As described above, Section 505(q)(3) of the Act requires that FDA submit an annual report to Congress containing statistical information regarding the number of ANDAs

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<sup>2</sup> Public Law 110-316, 122 Stat. 3509, 3524, section 301.

<sup>3</sup> Section 505(q)(1)(B).

<sup>4</sup> Section 505(q)(1)(C).

<sup>5</sup> Section 505(q)(1)(D).

and 505(b)(2) applications approved and the number of those applications delayed by 505(q) petitions during the reporting period.

**A. Reporting Period**

For purposes of this first annual report on delays in approvals, FDA has used the period from September 27, 2007 (date of enactment) through September 30, 2008. Future reports will be based on fiscal year data from October 1 through September 30.

**B. Information Included in the Report**

Section 505(q)(3) of the Act requires that FDA's report to Congress include the following information.

- **The number of applications that were approved during the preceding 12-month period**

From September 27, 2007, through September 30, 2008, 476 ANDAs and 31 505(b)(2) applications were approved.

- **The number of such applications whose effective dates were delayed by petitions referred to in paragraph (1) during such period**

The effective dates of only two ANDAs were delayed by 505(q) petitions<sup>6</sup> from September 27, 2007, through September 30, 2008.<sup>7</sup>

Both ANDAs were delayed by the same petitions, and the petitions were submitted by one of the ANDA sponsors, whose own ANDA was delayed as a result.<sup>8</sup> FDA made the decision to delay the approval of the pending ANDAs and, within 30 days, notified the ANDA applicants of the finding that delay of approval was necessary to protect the public health. To make this determination, the agency considered the following possible outcome:

If FDA approved the ANDAs before it completed the substantive review of the issues in the petitions and after further review, concluded that the petitioner's arguments against approval were meritorious, the presence on the market of drug products that did not meet the requirements for approval could negatively affect the public health.

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<sup>6</sup> This report does not provide data on pending applications whose effective dates may have been delayed by petitions that are not subject to section 505(q) of the Act because the reporting requirement in Section 505(q)(3)(B) references petitions submitted pursuant to 505(q)(1).

<sup>7</sup> FDA issued a third delay letter based on the same petitions for an ANDA relying on the same reference listed drug, but later determined that the ANDA was not ready for approval. Therefore, the petitions did not delay the approval of this ANDA.

<sup>8</sup> One petitioner submitted both a citizen petition and a petition for stay of Agency action on the same date.

No 505(b)(2) applications had approval delayed by 505(q) petitions during the reporting period.

- **The number of days by which such applications were so delayed**

After reviewing the two ANDAs delayed during the reporting period, FDA determined that each ANDA was delayed by 138 days because of the 505(q) petitions.

- **The number of such petitions that were submitted during such period**

The number of 505(q) petitions submitted from September 27, 2007, through September 30, 2008 was 21.

## **CONCLUSION**

FDA has had 1 year of experience implementing Section 505(q) and believes it is too soon to determine whether Section 505(q) is discouraging petitions submitted with the primary purpose of delaying approval of an ANDA or 505(b)(2) application. The requirement in section 505(q)(1)(F) for the agency to respond to Section 505(q) petitions within 180 days (and thus limit any delay of approval) may have this effect by itself.

Section 505(q) also may have some unintended outcomes. Several 505(q) petitions have been submitted by companies that hold approved ANDAs or that have ANDA or 505(b)(2) applications pending before FDA, rather than by innovator companies that hold the new drug application referenced by an ANDA or 505(b)(2) applicant. One example is the company that submitted the petitions resulting in the delay of approval of two ANDAs for this reporting period. The petitioner had an ANDA pending, and the petitions delayed approval of the petitioner's ANDA as well as a competitor's ANDA.

In addition, petitions that are filed early (i.e., many months or years before the potential approval of an ANDA or 505(b)(2) application for the targeted product) may not be subject to section 505(q) and its 180-day response deadline because no application for the product is pending when the petition is submitted.

FDA intends to monitor the petitions submitted under section 505(q). The goal is to implement an appropriate approach to petitions that will discourage those petitions that do not raise valid scientific issues and have the effect of improperly delaying approval of ANDAs or 505(b)(2) applications.

## **REPORT TO CONGRESS**

### **SECOND ANNUAL REPORT ON DELAYS IN APPROVALS OF APPLICATIONS RELATED TO CITIZEN PETITIONS AND PETITIONS FOR STAY OF AGENCY ACTION FOR FISCAL YEAR 2009**

#### **REQUIRED BY SECTION 914 OF THE FOOD AND DRUG ADMINISTRATION AMENDMENTS ACT**

**PUBLIC LAW 110-85**

**Department of Health and Human Services  
Food and Drug Administration**

## STATUTORY REQUIREMENT

The Food and Drug Administration Amendments Act (FDAAA) was enacted on September 27, 2007. Section 914 of Title IX of FDAAA took effect on the date of enactment and amended section 505 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355) by adding new subsection (q). Section 505(q) applies to certain petitions that request that FDA take any form of action related to a pending application submitted under section 505(b)(2) or 505(j) of the Act<sup>1</sup> and governs the manner in which these petitions are treated.

Section 505(q)(3) of the Act states:

- The Secretary shall annually submit to the Congress a report that specifies—
- (A) the number of applications that were approved during the preceding 12-month period;
  - (B) the number of such applications whose effective dates were delayed by petitions referred to in paragraph (1) during such period;
  - (C) the number of days by which such applications were so delayed; and
  - (D) the number of such petitions that were submitted during such period.

## I. BACKGROUND

### A. Citizen Petitions and Petitions for Stay of Agency Action

Citizen petitions are a vehicle that stakeholders outside of the Food and Drug Administration (FDA or the agency) can use to ask FDA to take (or refrain from taking) an action. For example, a petitioner can ask the agency to:

Disapprove a drug product application;  
Add warnings to a drug's label; and/or,  
Change products from prescription to over-the-counter (OTC) status.

FDA regulations provide the opportunity for any interested person to submit a citizen petition requesting FDA “to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action” (21 CFR 10.25 and 10.30). A petition can also be submitted to stay (delay) the effective date of any administrative action, such as the approval of a certain drug application (21 CFR

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<sup>1</sup> In this report, an application submitted under section 505(b)(2) of the Act is referred to as a *505(b)(2) application* and an application submitted under section 505(j) of the Act is referred to as an *abbreviated new drug application (ANDA)*.

10.35). Both citizen petitions and petitions for stay of agency action will be collectively referred to as “petitions” throughout this report.

## **B. Delays of Approvals**

Section 505(q)(1)(A), together with section 505(q)(5), describes the general scope of section 505(q). Section 505(q)(1)(A) provides:

The Secretary shall not delay approval of a pending application submitted under subsection (b)(2) or (j) because of any request to take any form of action relating to the application, either before or during consideration of the request, unless—

- (i) the request is in writing and is a petition submitted to the Secretary pursuant to section 10.30 or 10.35 of title 21, Code of Federal Regulations (or any successor regulations); and
- (ii) the Secretary determines, upon reviewing the petition, that a delay is necessary to protect the public health.

Consideration of the petition shall be separate and apart from review and approval of any application.<sup>2</sup>

In section 505(q)(5), the term *application* is defined as an application submitted under section 505(b)(2) or 505(j) of the Act and the term *petition* is defined as a request described in section 505(q)(1)(A)(i).

If FDA determines, based upon a request for action on a pending application, that a delay of approval of the abbreviated new drug application (ANDA) or 505(b)(2) application is necessary to protect the public health, FDA is required to provide to the applicant, not later than 30 days after making the determination, the following information:<sup>3</sup>

Notification that the determination has been made;

If applicable, any clarification or additional data that the applicant should submit to the petition docket to allow FDA to review the petition promptly; and

A brief summary of the specific substantive issues raised in the petition which form the basis of the determination.

At FDA’s discretion, the information is to be conveyed by either a document or a meeting with the applicant.<sup>4</sup> The information conveyed as part of the notification is to be considered part of the application and subject to applicable disclosure requirements.<sup>5</sup>

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<sup>2</sup> This sentence was added as a technical correction to FDAAA in Public Law 110-316, 122 Stat. 3509, 3524, section 301, enacted August 14, 2008.

<sup>3</sup> Section 505(q)(1)(B).

<sup>4</sup> Section 505(q)(1)(C).

<sup>5</sup> Section 505(q)(1)(D).

## II. STATUTORY REPORTING REQUIREMENT

As described above, section 505(q)(3) of the Act requires that FDA submit an annual report to Congress containing statistical information regarding the number of ANDAs and 505(b)(2) applications approved and the number of those applications delayed by 505(q) petitions during the reporting period. This second annual report complies with the requirement for fiscal year 2009.

### A. Reporting Period

This report is based on fiscal year data from October 1, 2008, through September 30, 2009.<sup>6</sup>

### B. Information Included in the Report

Section 505(q)(3) of the Act requires that FDA's report to Congress include the following information:

1. **The number of applications that were approved during the preceding 12-month period from October 1, 2008 through September 30, 2009:** 489 ANDAs and 35 505(b)(2) applications; and,
2. **The number of such applications whose effective dates were delayed by petitions referred to in paragraph (1):** One ANDA was delayed by a 505(q) petition<sup>7</sup> from October 1, 2008 through September 30, 2009.

FDA made the decision to delay the approval of the pending ANDA while it conducted an evaluation of the issues raised in the petition to determine whether a further delay of the approval of the ANDA was necessary to protect the public health under section 505(q)(1)(A)(ii). FDA considered whether the following outcome would be applicable in this case:

If FDA approved the ANDA before the agency completed the substantive review of the issues in the petitions and, after further review, concluded that the petitioner's arguments against approval were meritorious, the presence on the market of drug products that did not meet the requirements for approval could negatively affect the public health.

Once the FDA completed its review of the issues raised by the petition, it determined that further delay of approval of the ANDA was not necessary to

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<sup>6</sup> The first annual report covered the period from the date of enactment (September 27, 2007) through September 30, 2008.

<sup>7</sup> This report does not provide data on pending applications whose effective dates may have been delayed by petitions that are not subject to section 505(q) of the Act (see section 505(q)(3)(B) referencing petitions referred to in paragraph (1)).

protect the public health, and the agency approved the ANDA prior to issuing a response to the petition.

No 505(b)(2) applications had approval delayed by 505(q) petitions during the reporting period.

3. **The number of days by which such applications were so delayed:** After reviewing the ANDA delayed during the reporting period, FDA determined that the ANDA was delayed by 27 days because of the 505(q) petition; and,
4. **The number of such petitions that were submitted during such period:** The number of 505(q) petitions submitted from October 1, 2008, through September 30, 2009, was 31.

### III. CONCLUSION

FDA continues to work to implement the provisions of section 505(q). In January 2009, the agency issued a draft guidance for industry entitled: *Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act*. This draft guidance addresses the following topics:

Information regarding FDA's current thinking on interpreting section 505(q) regarding how FDA determines (1) if the provisions of section 505(q) addressing the treatment of petitions apply to a particular petition and (2) if a petition would delay approval of a pending ANDA or 505(b)(2) application;

How FDA interprets the provisions of section 505(q) requiring (1) that a petition include a certification and (2) that supplemental information or comments to a petition include a verification; and,

The relationship between the review of petitions and the review of pending ANDAs and 505(b)(2) applications for which FDA has not yet made a decision on approvability.

FDA also is considering issuing regulations through notice-and-comment rulemaking to further implement section 505(q).

Although FDA now has 2 years of experience implementing section 505(q), it believes it may still be too early to make a determination as to whether section 505(q) is effectively discouraging petitions submitted with the primary purpose of delaying approval of an ANDA or 505(b)(2) application. FDA notes, however, that the number of 505(q) petitions submitted during fiscal year 2009 increased by more than 47 percent over the number submitted during the first reporting period. FDA has met the 180-day timeframes for these petitions by redirecting efforts previously directed to other work.

During the period from October 1, 2008 through September 30, 2009, FDA responded to 23 petitions subject to section 505(q) within the 180-day statutory timeframe. FDA

responded to two additional petitions where the statutory timeframe was missed. The number of applications that have been delayed by petitions subject to section 505(q) is extremely low — three ANDAs and no 505(b)(2) applications in 2 years. In a few instances, FDA has responded to 505(q) petitions earlier than required by the statutory timeframe because a related application was ready for approval. In most instances, however, the statutory deadline for responding to a 505(q) petition has occurred before any related ANDAs or 505(b)(2) applications were ready for approval.

FDA continues to monitor closely the petitions submitted under section 505(q) and notes the following areas of concern:

FDA continues to receive 505(q) petitions from ANDA and 505(b)(2) applicants and not solely from innovator companies;

FDA is seeing an increase in petitions for reconsideration pursuant to 21 CFR 10.33, requiring the agency to readdress issues that have already been decided; and

FDA has also received serial 505(q) petitions frequently from the same petitioner about a specific drug product or class of drug products, sometimes resulting in several petition responses about different aspects of the same product.

If these areas of concern become trends, they may undermine the goal of discouraging the submission of petitions that do not raise valid scientific issues and have the effect of improperly delaying approval of ANDAs or 505(b)(2) applications.

## **REPORT TO CONGRESS**

### **THIRD ANNUAL REPORT ON DELAYS IN APPROVALS OF APPLICATIONS RELATED TO CITIZEN PETITIONS AND PETITIONS FOR STAY OF AGENCY ACTION FOR FISCAL YEAR 2010**

#### **REQUIRED BY SECTION 914 OF THE FOOD AND DRUG ADMINISTRATION AMENDMENTS ACT**

**PUBLIC LAW 110-85**

**Department of Health and Human Services  
Food and Drug Administration**

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Margaret A. Hamburg, M.D.  
Commissioner of Food and Drugs

Date \_\_\_\_\_

## **I. STATUTORY REQUIREMENT**

The Food and Drug Administration Amendments Act (FDAAA) was enacted on September 27, 2007. Section 914 of Title IX of FDAAA took effect on the date of enactment and amended section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) by adding new subsection (q). Section 505(q) applies to certain petitions that request that Food and Drug Administration (FDA) take any form of action related to a pending drug application submitted under section 505(b)(2) or 505(j) of the FD&C Act and governs the manner in which these petitions are treated.<sup>1</sup>

Section 505(q)(3) of the FD&C Act states that:

The Secretary shall annually submit to the Congress a report that specifies –

- (A) the number of applications that were approved during the preceding 12-month period;
- (B) the number of such applications whose effective dates were delayed by petitions referred to in [505(q)(1) of the FD&C Act] during such period;
- (C) the number of days by which such applications were so delayed; and
- (D) the number of such petitions that were submitted during such period.

FDA is submitting this report to satisfy the obligations set forth in Section 505(q)(3).

## **II. BACKGROUND**

### **A. Citizen Petitions and Petitions for Stay of Agency Action**

A citizen petition is a vehicle that stakeholders outside of FDA can use to ask FDA “to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action” (21 CFR 10.25 and 10.30). Pursuant to the governing regulations, petitioners can request, for example, that the agency:

- Disapprove a drug product application;
- Add warnings to a drug’s label; or
- Change products from prescription to over-the-counter (OTC) status.

FDA regulations also provide for the submission of petitions for “stay of action” to delay the effective date of an administrative action, such as the approval of a certain

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<sup>1</sup> In this report, an application submitted under section 505(b)(2) of the FD&C Act is referred to as a *505(b)(2) application*, and an application submitted under section 505(j) of the FD&C Act is referred to as an *abbreviated new drug application (ANDA)*.

drug application (21 CFR 10.35). Both citizen petitions and petitions for stay of agency action will be collectively referred to as “petitions” throughout this report, and petitions subject to section 505(q) of the FD&C Act will be referred to as “505(q) petitions.”

## **B. Delays of Approvals**

Section 505(q)(1)(A), together with section 505(q)(5), describes the general scope of section 505(q). Section 505(q)(1)(A) provides:

The Secretary shall not delay approval of a pending application submitted under subsection (b)(2) or (j) because of any request to take any form of action relating to the application, either before or during consideration of the request, unless—

- (i) the request is in writing and is a petition submitted to the Secretary pursuant to section 10.30 or 10.35 of title 21, Code of Federal Regulations (or any successor regulations); and
- (ii) the Secretary determines, upon reviewing the petition, that a delay is necessary to protect the public health.

Consideration of the petition shall be separate and apart from review and approval of any application.<sup>2</sup>

In section 505(q)(5), the term *application* is defined as an application submitted under section 505(b)(2) or 505(j) of the FD&C Act, and the term *petition* is defined as a request described in section 505(q)(1)(A)(i) (*i.e.*, a written request submitted in accordance with 21 CFR 10.30 or 10.35).

If FDA determines, based on a petition requesting action on a pending ANDA or 505(b)(2) application, that a delay of approval of a pending application is necessary to protect the public health, FDA is required to provide to the applicant, not later than 30 days after making the determination, the following information:

- Notification that the determination has been made;
- If applicable, any clarification or additional data that the applicant should submit to the petition docket to allow FDA to review the petition promptly; and
- A brief summary of the specific substantive issues raised in the petition which form the basis of the determination.<sup>3</sup>

At FDA’s discretion, the information described above is to be conveyed to the applicant either in a written document or through a meeting with the applicant.<sup>4</sup> The

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<sup>2</sup> This sentence was added as a technical correction to FDAAA in Public Law 110-316, 122 Stat. 3509, 3524, section 301, enacted August 14, 2008.

<sup>3</sup> Section 505(q)(1)(B).

<sup>4</sup> Section 505(q)(1)(C).

information conveyed as part of the notification is to be considered part of the application and subject to applicable disclosure requirements.<sup>5</sup>

### **III. INFORMATION REPORTED**

Section 505(q)(3) of the FD&C Act requires FDA to submit an annual report to Congress containing certain statistical information regarding the approval of ANDAs and 505(b)(2) applications and the effect, if any, that 505(q) petitions have had on the timing of such approvals. This annual report complies with the statutory reporting requirements for fiscal year 2010, based on data from October 1, 2009, through September 30, 2010.

The statute requires the following information to be included in the report:

- The number of ANDAs and 505(b)(2) applications approved during the reporting period;
- The number of such applications that were delayed by 505 (q) petitions;
- The number of days by which such applications were so delayed; and
- The number of 505(q) petitions that were submitted during the reporting period.

During the FY 2010 reporting period, the agency approved 29 505(b)(2) applications and 426 ANDAs. No 505(b)(2) approvals were delayed because of the filing of a 505(q) petition. One ANDA approval was delayed by nine days because of a pending 505(q) petition. Twenty 505(q) petitions were filed during the reporting period. FDA did not miss the statutory deadline for responding to any 505(q) petitions during this reporting period.

FDA's decision to delay the approval of one pending ANDA by nine days was based on the agency's assessment that further review of the issues raised in the 505(q) petition was required to fully assess the petitioners' arguments against approval. FDA was concerned that if it approved the ANDA before resolving the issues raised in the petition and later concluded that one or more of the arguments against approval were meritorious, then the presence on the market of drug products that did not meet the requirements for approval could negatively affect the public health. Thus, FDA decided to delay approval of the product at issue for an additional nine days to complete its analysis of the petition. After FDA completed its review, the agency determined that further delay of approval of the ANDA was not necessary to protect the public health, and the agency approved the ANDA prior to issuing a response to the petition.

### **IV. IMPLEMENTATION DISCUSSION**

FDA has been implementing the provisions of section 505(q) for approximately three years. We did so both by issuing draft guidance to encourage industry to use the 505(q) process appropriately and by reviewing and responding to the more than 70 505(q) petitions that have been filed during the three-year period.

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<sup>5</sup> Section 505(q)(1)(D).

**a. Guidance.**

In January 2009, the agency issued a draft guidance for industry titled: *Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act*. This draft guidance addresses the agency's current thinking on following topics:

- How FDA determines whether a particular petition would delay approval of a pending ANDA or 505(b)(2) application and, therefore, would fall within section 505(q);
- How FDA interprets the certification and verification requirements under section 505(q); and
- The relationship between the review of petitions and the review of pending ANDAs and 505(b)(2) applications for which FDA has not yet made a decision on approvability.

FDA plans to finalize this guidance in 2011.

**b. Petition Review and Observations**

During fiscal years (FY) 2008 through 2010, FDA received a total of 72 505(q) petitions (21 in FY 2008, 31 in FY 2009, and 20 in FY 2010). Over this three year period, FDA responded to all but two 505(q) petitions within the 180-day statutory timeframe. In certain circumstances, FDA has responded to 505(q) petitions earlier than required by the statutory timeframe to avoid unnecessary delays in product approval.

FDA continues to monitor the number and nature of 505(q) petitions filed and to analyze whether section 505(q) is effectively discouraging petitioners from submitting petitions primarily to delay the approval of ANDAs or 505(b)(2) applications. FDA also is closely monitoring the effect of 505(q) petitions, and the 180-day statutory response period for these petitions, on the other work of the agency. FDA has consistently met the statutory deadlines by redirecting efforts that otherwise would have been directed to other work, including responding to other citizen petitions. Although we now have three years of experience implementing section 505(q), we do not believe that the data are sufficient to determine whether section 505(q) is having its intended effect.

Some of the trends in 505(q) petitions that we believe may be relevant are as follows:

- Over the three year period during which we have been reviewing 505(q) petitions, the number of applications that have been delayed due to analysis of the issues raised in the 505(q) petitions is low: 4 ANDAs and no 505(b)(2) applications.

- FDA continues to receive 505(q) petitions from ANDA and 505(b)(2) applicants, and not solely from innovator companies.
- In many instances, the statutory deadline for responding to a 505(q) petition occurs before any related ANDAs or 505(b)(2) applications are ready for approval.
- FDA has received serial 505(q) petitions, frequently from the same petitioner, about the same specific drug or class of drugs, sometimes requiring several separate responses about different aspects of the same product. In the current reporting period, for example, the agency received its fourth 505(q) petition relating to the approval of ANDAs for the anti-depressant venlafaxine hydrochloride. These submissions were spread out over a period of 24 months (with filing dates of May 2008, July 2009, August 2009, and May 2010), and each petition raised different scientific issues. The agency responded to all four petitions within the 180-day statutory deadline. Responding to such serial petitions requires the use of substantial FDA resources, on a repeated basis, over a protracted period of time.
- Since the passage of FDAAA, FDA has seen an increase in petitions for reconsideration of the agency's denial of 505(q) petitions, requiring the agency to readdress issues that already have been decided.

As noted above, FDA believes that additional experience and trend data are required to determine whether section 505(q) is accomplishing the stated goals of the legislation. Based on the petitions that we have seen to date, however, the agency is concerned that section 505(q) may not be discouraging the submission of petitions that do not raise valid scientific issues and are intended primarily to delay the approval of competitive drug products. We also believe that innovator companies may be implementing strategies to file serial 505(q) petitions and petitions for reconsideration in an effort to delay approval of ANDAs or 505(b)(2) applications for competing drugs. We will continue to monitor and analyze the 505(q) landscape and will provide further analysis in our next annual report.

## **REPORT TO CONGRESS**

### **Fourth Annual Report on Delays in Approvals of Applications Related to Citizen Petitions and Petitions for Stay of Agency Action for Fiscal Year 2011**

**Required by Section 914 of the Food and Drug Administration Amendments  
Act**

**Public Law 110-85**

**Department of Health and Human Services  
Food and Drug Administration**

## **I. STATUTORY REQUIREMENT**

The Food and Drug Administration Amendments Act (FDAAA) was enacted on September 27, 2007. Section 914 of Title IX of FDAAA took effect on the date of enactment and amended section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) by adding new subsection (q). Section 505(q) applies to certain petitions that request that the Food and Drug Administration (FDA) take any form of action related to a pending drug application submitted under section 505(b)(2) or 505(j) of the FD&C Act and governs the manner in which these petitions are treated.<sup>1</sup>

Section 505(q)(3) of the FD&C Act states that:

The Secretary shall annually submit to the Congress a report that specifies:

- (A) the number of applications that were approved during the preceding 12-month period;
- (B) the number of such applications whose effective dates were delayed by petitions referred to in [505(q)(1) of the FD&C Act] during such period;
- (C) the number of days by which such applications were so delayed; and
- (D) the number of such petitions that were submitted during such period.

FDA is submitting this report to satisfy the obligations set forth in section 505(q)(3).

## **II. BACKGROUND**

### **A. Citizen Petitions and Petitions for Stay of Agency Action**

A citizen petition is a vehicle that stakeholders outside of FDA can use to ask FDA “to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action” (21 CFR 10.25 and 10.30). Pursuant to the governing regulations, petitioners can request, for example, that the agency:

- Disapprove a drug product application;
- Add warnings to the labeling of a drug; and/or
- Change products from prescription to over-the-counter (OTC) status.

FDA regulations also provide for the submission of petitions for “stay of action” to delay the effective date of an administrative action, such as the approval of certain drug application (21 CFR 10.35). Both citizen petitions and petitions for stay of agency action will be collectively referred to as “petitions” throughout this report, and

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<sup>1</sup> In this report, an application submitted in accordance with section 505(b)(2) of the FD&C Act is referred to as a *505(b)(2) application*, and an application submitted under section 505(j) of the FD&C Act is referred to as an *abbreviated new drug application (ANDA)*.

petitions subject to section 505(q) of the FD&C Act will be referred to as “505(q) petitions.”

## **B. Delays of Approvals**

Section 505(q)(1)(A), together with section 505(q)(5), describes the general scope of section 505(q). Section 505(q)(1)(A) provides:

The Secretary shall not delay approval of a pending application submitted under subsection (b)(2) or (j) because of any request to take any form of action relating to the application, either before or during consideration of the request, unless:—

- (i) the request is in writing and is a petition submitted to the Secretary pursuant to section 10.30 or 10.35 of title 21, Code of Federal Regulations (or any successor regulations); and
- (ii) the Secretary determines, upon reviewing the petition, that a delay is necessary to protect the public health.

Consideration of the petition shall be separate and apart from review and approval of any application.<sup>2</sup>

In section 505(q)(5), the term *application* is defined as an application submitted under section 505(b)(2) or 505(j) of the FD&C Act, and the term *petition* is defined as a request described in section 505(q)(1)(A)(i) (*i.e.*, a written request submitted in accordance with 21 CFR 10.30 or 10.35).

If FDA determines, based on a petition requesting action on a pending abbreviated new drug application (ANDA) or 505(b)(2) application, that a delay of approval of a pending application is necessary to protect the public health, FDA is required to provide to the applicant, not later than 30 days after making the determination, the following information:

- Notification that the determination has been made;
- If applicable, any clarification or additional data that the applicant should submit to the petition docket to allow FDA to review the petition promptly; and
- A brief summary of the specific substantive issues raised in the petition which form the basis of the determination.<sup>3</sup>

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<sup>2</sup> This sentence was added as a technical correction to FDAAA in Public Law 110-316, 122 Stat. 3509, 3524, section 301, enacted August 14, 2008.

<sup>3</sup> FD&C Act, section 505(q)(1)(B).

At FDA's discretion, the information described above is to be conveyed to the applicant either in a written document or through a meeting with the applicant.<sup>4</sup> The information conveyed as part of the notification is to be considered part of the application and subject to applicable disclosure requirements.<sup>5</sup>

### **III. INFORMATION REPORTED**

Section 505(q)(3) of the FD&C Act requires FDA to submit an annual report to Congress containing certain statistical information regarding the approval of ANDAs and 505(b)(2) applications and the effect, if any, that 505(q) petitions have had on the timing of such approvals. This annual report complies with the statutory reporting requirements for fiscal year (FY) 2011, based on data from October 1, 2010, through September 30, 2011.

The statute requires the following information to be included in the report:

- The number of ANDAs and 505(b)(2) applications approved during the reporting period;
- The number of such applications that were delayed by 505(q) petitions;
- The number of days by which such applications were so delayed; and
- The number of 505(q) petitions that were submitted during the reporting period.

Between September 27, 2007 and September 30, 2011, FDA determined that a delay in approving an ANDA was necessary to protect the public health in the case of 5 ANDAs with related 505(q) petitions. FDA has not delayed approval of any 505(b)(2) applications based on 505(q) petitions.

During the FY 2011 reporting period, the agency approved 43 applications submitted under section 505(b)(2) and 458 ANDAs. No 505(b)(2) approvals were delayed because of the filing of a 505(q) petition in this reporting period. One ANDA approval was delayed by 78 days because of pending 505(q) petitions.

FDA's decision to delay the approval of one pending ANDA during this reporting period was based on the agency's assessment that further review of the issues raised in the 505(q) petitions was required to fully assess the petitioners' arguments against approval. FDA was concerned that if it approved the ANDA before resolving the issues raised in the petitions and later concluded that one or more of the arguments against approval were meritorious, then the presence on the market of drug products that did not meet the requirements for approval could negatively affect public health. Thus, FDA decided to delay approval of the product at issue for 78 days to complete its analysis of the issues raised in the petitions. After FDA completed its review, the agency determined that further delay of approval of the ANDA was not necessary to protect the public health, and the agency approved the ANDA on the same day a response to the petitions was issued. This delay had no impact on the marketing of the product because, as a result of a

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<sup>4</sup> FD&C Act, section 505(q)(1)(C).

<sup>5</sup> FD&C Act, section 505(q)(1)(D).

court's patent decision, the holder of the ANDA is enjoined from marketing the product for several years.

During the FY 2011 reporting period, 20 petitions considered 505(q) petitions were submitted to the agency. FDA did not miss the statutory deadline for responding to any 505(q) petitions during this reporting period.

#### **IV. IMPLEMENTATION DISCUSSION**

FDA has been implementing the provisions of section 505(q) for approximately 4 years. FDA has done so both by issuing guidance to encourage industry to use the 505(q) process appropriately and by reviewing and responding to the more than 90 petitions subject to section 505(q) that have been filed during the 4-year period.

##### **A. Guidance.**

In January 2009, the agency issued draft guidance for industry titled: *Citizen Petitions and Petitions for Stay of Action Subject to section 505(q) of the Federal Food, Drug, and Cosmetic Act*. In June 2011 FDA issued the final guidance ([www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079353.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079353.pdf)). The final guidance addresses the agency's current thinking on the following topics:

- How FDA determines whether a particular petition would delay approval of a pending ANDA or 505(b)(2) application and, therefore, would fall within section 505(q);
- How FDA interprets the certification and verification requirements under section 505(q); and
- The relationship between the review of petitions and the review of pending ANDAs and 505(b)(2) applications for which FDA has not yet made a decision on approvability.

##### **B. Petition Review and Observations**

During FY 2008 through FY 2011, FDA received a total of 92 petitions subject to section 505(q) (21 in FY 2008, 31 in FY 2009, 20 in FY 2010, and 20 in FY 2011). Over this 4-year period, FDA responded to all but 2 of the 505(q) petitions within the 180-day statutory timeframe that was applicable during that period.<sup>6</sup> In certain circumstances FDA responded to 505(q) petitions earlier than required by the statutory time frame to avoid unnecessary delays in product approval. As an example, in October 2010 FDA received a petition regarding generic versions of

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<sup>6</sup> The 180-day statutory timeframe for responding to 505(q) petitions was reduced to 150 days by section 1135 of the Food and Drug Administration Safety and Innovation Act.

Xyzal. The petitioner requested that FDA refrain from granting final approval for any ANDA for a generic version of Xyzal (levocetirizine dihydrochloride) if the ANDA includes proposed labeling that omits or carves out Xyzal's indications for seasonal allergic rhinitis (SAR) and perennial allergic rhinitis (PAR). On February 24, 2011, FDA responded to the petition before the statutory deadline of April 13, 2011. As mentioned in the response, on the same day FDA approved two ANDAs for chronic idiopathic urticaria with labeling that did not include information about the use of Xyzal for the PAR and SAR indications.

FDA continues to monitor the number and nature of 505(q) petitions filed and to analyze whether section 505(q) is effectively discouraging petitioners from submitting petitions primarily to delay the approval of ANDAs or 505(b)(2) applications. FDA is also closely monitoring the effect of 505(q) petitions, and the statutory response period for these petitions, on the other work of the agency; FDA consistently met the statutory deadlines by redirecting efforts that otherwise would have been directed to other work, including responding to other citizen petitions.

It is difficult to determine whether section 505(q) is discouraging the filing of citizen petitions aimed at blocking generic competition. However, since the passage of FDAAA, the number of 505(q) petitions submitted annually has been steady – in 3 out of 4 fiscal years, FDA received approximately 20 such petitions:

<u>FY</u>	<u>No. of Petitions</u>	<u>No. of 505(q) petitions</u>	<u>% of 505(q)/all petitions</u>
'08	78	21	26.92
'09	81	31	38.27
'10	76	20	26.32
'11	96	20	20.83

Some of the trends in 505(q) petitions that FDA believes may be relevant are as follows:

- In many instances the statutory deadline for responding to a 505(q) petition occurs before any related ANDAs or 505(b)(2) applications are ready for approval. Accordingly, a relatively small percentage of applications are delayed by these petitions.
- Over the 4-year period during which FDA has been reviewing 505(q) petitions, approximately 5% of the petitions resulted in a delay in approving an ANDA.
- FDA continues to receive 505(q) petitions from ANDA and 505(b)(2) applicants, and not solely from innovator companies.

- FDA has received serial 505(q) petitions, frequently from the same petitioner, about the same specific drug or class of drugs, sometimes requiring several separate responses about different aspects of the same product. In addition, petitioners are raising their arguments serially, rather than asserting all available arguments in the first petition filed. In the FY 2011 reporting period, for example, the agency received its fourth 505(q) petition relating to the approval of ANDAs for topical ophthalmic products and a third 505(q) petition related to Doryx (doxycycline). The various submissions raised different scientific issues, requiring serial review of different arguments, rather than one comprehensive review of all pertinent arguments. The agency responded to all of these petitions within the statutory deadline. Responding to such serial petitions requires the use of substantial FDA resources, on a repeated basis, over a protracted period of time.

FDA will continue to gain additional experience and monitor trend data in the FY 2012 reporting period to assist Congress in determining whether section 505(q) is accomplishing the stated goals of the legislation. Based on the petitions that FDA has seen to date, however, the agency is concerned that section 505(q) may not be discouraging the submission of petitions that do not raise valid scientific issues and are intended primarily to delay the approval of competitive drug products. Though many 505(q) petitions do not necessarily raise issues that are important to the public health, the statute requires FDA to prioritize these petitions above other matters, such as safety petitions, that do raise important public health concerns. FDA also believes that innovator companies may be implementing strategies to file serial 505(q) petitions and petitions for reconsideration in an effort to delay approval of ANDAs or 505(b)(2) applications for competing drugs. FDA remains concerned about the resources required to respond to 505(q) petitions within the statutory deadline at the expense of completing the other work of the agency.

## **REPORT TO CONGRESS**

### **Fifth Annual Report on Delays in Approvals of Applications Related to Citizen Petitions and Petitions for Stay of Agency Action for Fiscal Year 2012**

**Required by Section 914 of the Food and Drug Administration Amendments Act**

**Public Law 110-85**

**Department of Health and Human Services  
Food and Drug Administration**

\_\_\_\_\_  
Margaret A. Hamburg, M.D.  
Commissioner of Food and Drugs

Date \_\_\_\_\_

## I. STATUTORY REQUIREMENT

The Food and Drug Administration Amendments Act (FDAAA) was enacted on September 27, 2007. Section 914 of Title IX of FDAAA took effect on the date of enactment and amended section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) by adding new subsection (q). Section 505(q) applies to certain petitions that request that the Food and Drug Administration (FDA or agency) take any form of action related to a pending drug approval application submitted under section 505(b)(2) or 505(j) of the FD&C Act or section 351(k) of the Public Health Service Act (PHS Act).<sup>1</sup> Section 505(q) also governs the manner in which these petitions are treated.

The Food and Drug Administration Safety and Innovation Act (FDASIA) was signed into law on July 9, 2012 (Pub. L. 112-144, 126 Stat. 993). Section 1135 of FDASIA amended section 505(q) of the FD&C Act in two ways. First, it shortened FDA's deadline from 180 days to 150 days for responding to petitions subject to section 505(q). Second, it expanded the scope of section 505(q) to include certain petitions concerning applications submitted under section 351(k) of the PHS Act, the abbreviated pathway for the approval of biosimilar biological products. Accordingly, we are now including biosimilar biological product applications in the annual report on delays in approvals by petitions, as required under section 914 of FDAAA.

Under Section 505(q)(3) of the FD&C Act, FDA is required to submit an annual report to Congress.

## II. BACKGROUND

### A. Citizen Petitions and Petitions for Stay of Agency Action

A citizen petition is a vehicle that stakeholders outside of FDA can use to ask FDA "to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action" (21 CFR 10.25(a) and 10.30). Under the governing regulations, petitioners can request, for example, that the agency:

- Disapprove a drug product application;
- Add warnings to the labeling of a drug; and/or
- Change products from prescription to over-the-counter (OTC) status.

FDA regulations also provide for the submission of petitions for "stay of action" to delay the effective date of an administrative action, such as the approval of certain drug applications (21 CFR 10.35). In this report, we will collectively refer to both citizen petitions and petitions for stay of agency action as "petitions" and will refer to petitions subject to section 505(q) of the FD&C Act as "505(q) petitions."

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<sup>1</sup> In this report, an application submitted in accordance with section 505(b)(2) of the FD&C Act is referred to as a *505(b)(2) application*; an application submitted under section 505(j) of the FD&C Act is referred to as an *abbreviated new drug application (ANDA)*; and an application submitted under section 351(k) of the PHS Act is referred to as a *biosimilar biological product application*.

## B. Delays of Approvals

Section 505(q)(1)(A), together with section 505(q)(5), describes the general scope of section 505(q). Section 505(q)(1)(A) provides:

The Secretary shall not delay approval of a pending application submitted under subsection (b)(2) or (j) of [section 505 of the FD&C Act] or section 351(k) of the Public Health Service Act because of any request to take any form of action relating to the application, either before or during consideration of the request, unless—

- (i) the request is in writing and is a petition submitted to the Secretary pursuant to section 10.30 or 10.35 of title 21, Code of Federal Regulations (or any successor regulations); and
- (ii) the Secretary determines, upon reviewing the petition, that a delay is necessary to protect the public health.

Consideration of the petition shall be separate and apart from review and approval of any application.<sup>2</sup>

In section 505(q)(5), the term *application* is defined as an application submitted under section 505(b)(2) or 505(j) of the FD&C Act or section 351(k) of the PHS Act, and the term *petition* is defined as a request described in section 505(q)(1)(A)(i) (i.e., a written request submitted in accordance with 21 CFR 10.30 or 10.35).

If FDA determines, based on a petition requesting action on a pending abbreviated new drug application (ANDA), 505(b)(2) application, or biosimilar biological product application, that a delay of approval of a pending application is necessary to protect the public health, FDA is required to provide to the applicant, not later than 30 days after making the determination, the following information:

- Notification that the determination has been made;
- If applicable, any clarification or additional data that the applicant should submit to the petition docket to allow FDA to review the petition promptly; and
- A brief summary of the specific substantive issues raised in the petition which form the basis of the determination.<sup>3</sup>

At FDA's discretion, the information described above is to be conveyed to the applicant either in a written document or through a meeting with the applicant.<sup>4</sup> The information conveyed as part of the notification is to be considered part of the application and subject to applicable disclosure requirements.<sup>5</sup>

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<sup>2</sup> This sentence was added as a technical correction to FDAAA in Public Law 110-316, 122 Stat. 3509, 3524, section 301, enacted August 14, 2008.

<sup>3</sup> FD&C Act, section 505(q)(1)(B).

<sup>4</sup> FD&C Act, section 505(q)(1)(C).

<sup>5</sup> FD&C Act, section 505(q)(1)(D).

### **III. INFORMATION REPORTED**

Section 505(q)(3) of the FD&C Act requires FDA to submit an annual report to Congress containing statistical information regarding the approval of certain applications and the effect, if any, that 505(q) petitions have had on the timing of such approvals. Biosimilar biologics licensing applications are included in this fiscal year (FY) 2012 annual report as a result of amendments to section 505(q)(3) of the FD&C Act enacted by FDASIA. This annual report complies with the statutory reporting requirements for FY 2012, based on data from October 1, 2011, through September 30, 2012.

The statute requires the following information to be included in the report:

- The number of ANDAs, 505(b)(2) applications, and biosimilar biological product applications approved during the reporting period;
- The number of such applications that were delayed by 505(q) petitions;
- The number of days by which the applications were delayed; and
- The number of 505(q) petitions that were submitted during the reporting period.

Between September 27, 2007, and September 30, 2012, FDA determined that a delay in approving an ANDA was necessary to protect the public health in the case of five ANDAs with related 505(q) petitions. FDA has not delayed approval of any 505(b)(2) applications or biosimilar biological product applications based on 505(q) petitions.

During the FY 2012 reporting period, the agency approved 42 applications submitted under section 505(b)(2), 517 ANDAs, and no biosimilar biological product applications. No approvals for any 505(b)(2) or biosimilar biological product applications were delayed because of the filing of a 505(q) petition in this reporting period. No ANDA approvals were delayed in this reporting period because of pending 505(q) petitions.

During the FY 2012 reporting period, 24 petitions considering 505(q) petitions were submitted to the agency. FDA did not miss the statutory deadline for responding to any 505(q) petitions during this reporting period.

### **IV. IMPLEMENTATION DISCUSSION**

FDA has been implementing the provisions of section 505(q) for approximately 5 years. FDA has done so by issuing guidance to encourage industry to use the 505(q) process appropriately, by proposing a regulation, and by reviewing and responding to the more than 100 petitions subject to section 505(q) that have been submitted during the 5-year period.

## **A. Guidance**

In January 2009, the agency issued draft guidance for industry titled: *Citizen Petitions and Petitions for Stay of Action Subject to section 505(q) of the Federal Food, Drug, and Cosmetic Act*. In June 2011, FDA issued the final guidance ([www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079353.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079353.pdf)). The final guidance addresses the agency's current thinking on the following topics:

- How FDA determines whether a particular petition would delay approval of a pending ANDA or 505(b)(2) application and, therefore, would fall within section 505(q);
- How FDA interprets the certification and verification requirements under section 505(q); and
- The relationship between the review of petitions and the review of pending ANDAs and 505(b)(2) applications for which FDA has not yet made a decision on approvability.

FDA is evaluating the impact of FDASIA on the recommendations in the final guidance.

## **B. Proposed Regulation**

In January 2012 (77 FR 25), FDA published a proposed rule titled *Amendments to Regulations on Citizen Petitions, Petitions for Stay of Action, and Submission of Documents to Dockets*. The proposed rule outlined proposed amendments to certain regulations relating to citizen petitions, petitions for stay of action, and submission of documents to the agency. FDA proposed to add new § 10.31 (21 CFR 10.31), which includes the following provisions:

- Proposed § 10.31(a) states that § 10.31 would encompass all citizen petitions and petitions for stay of action that request that the agency take any action that could, if taken, delay approval of an ANDA or 505(b)(2) application (i.e., citizen petitions and petitions for stay of action that are or may be subject to section 505(q) of the FD&C Act).
- Proposed § 10.31(b) would clarify the date of submission for petitions submitted under § 10.31.
- Proposed § 10.31(c) and (d) would codify the certification and verification requirements of section 505(q)(1)(H) and (I).

The comment period for this proposed rule has closed, and FDA currently is reviewing all of the comments submitted. FDA also is evaluating the impact of FDASIA on the provisions proposed in this rulemaking.

## **C. Petition Review and Observations**

During FY 2008 through FY 2012, FDA received a total of 116 petitions subject to section 505(q) (21 in FY 2008, 31 in FY 2009, 20 in FY 2010, 20 in FY 2011, and 24 in FY 2012). Over this 5-year period, FDA responded to all but 2 of the 505(q) petitions within the 180-day statutory time frame that was applicable during that period.<sup>6</sup>

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<sup>6</sup> The 180-day statutory time frame for responding to 505(q) petitions was reduced to 150 days by section

FDA continues to monitor the number and nature of 505(q) petitions submitted and to analyze whether section 505(q) is effectively discouraging petitioners from submitting petitions primarily to delay the approval of applications. FDA also is closely monitoring the effect of 505(q) petitions and the statutory response period for these petitions on the other work of the agency. Although FDA consistently met the statutory deadlines, it did so in part by redirecting efforts that otherwise would have been directed to other work, including responding to other citizen petitions.

It is difficult to determine whether section 505(q) is discouraging the filing of citizen petitions aimed at blocking generic competition. However, since the passage of FDAAA, the number of 505(q) petitions submitted annually has been steady—in 4 out of 5 fiscal years, FDA received approximately 20 such petitions. Table 1 shows the percentage of 505(q) petitions received as of September 30, 2012.

Table 1  
Percentage of 505(q) Petitions Received  
During Fiscal Years 2008-2012

FY	No. of Petitions <sup>7</sup>	No. of 505(q) petitions	% of 505(q)/all petitions
'08	78	21	26.92
'09	81	31	38.27
'10	76	20	26.32
'11	96	20	20.83
'12	94	24	25.53

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1135 of FDASIA.

<sup>7</sup> This represents the number of petitions handled by the Center for Drug Evaluation and Research, excluding suitability petitions and petitions that raise only OTC monograph issues.

Table 2 below summarizes the outcomes for the 97 petitions that have been resolved under section 505(q) as of September 30, 2012.

Table 2  
Outcomes Of 505(q) Petitions  
Resolved During Fiscal Years 2008-2012

	FY	Denied	Granted	Granted /Denied in Part	Withdrawn	Total # of Determinations
Fiscal Year	'08	10	1	3	0	14
	'09	16	2	6	0	24
	'10	16	2	6	0	24
	'11	10	1	9	2	22
	'12	10	1	2	0	13*
	Total	62	7	26	2	<b>97</b>

\* The number of petitions submitted affects the number of determinations. The total number of determinations in FY '12 was less than in other years because fewer petitions were submitted during the preceding months. We met the 505(q) deadline for all petitions resolved during FY '12.

Outcomes:

- **Denied**: FDA denied the requested actions outlined in the petition. This includes instances where FDA issued a denial without comment to the substance of a request.
- **Granted**: FDA granted the requested actions outlined in the petition.
- **Granted in Part, Denied in Part**: FDA denied some of the requested actions and granted some of the requested actions in the petition. This includes instances where FDA denied one or more of the requests without comment to the substance of a request.
- **Withdrawn**: The petitioner withdrew the petition.

As of September 30, 2012, 62 of the petitions (approximately 64%) responded to under section 505(q) have been denied. Another 26 petitions (approximately 27%) have been denied in part and granted in part. Only 7 petitions (approximately 7%) have been granted. An additional 2 petitions, approximately 2%, were voluntarily withdrawn by the petitioner.

Some of the trends in 505(q) petitions that FDA believes may be relevant are as follows:

- In many instances, the statutory deadline for responding to a 505(q) petition occurs before any related ANDAs or 505(b)(2) applications are ready for approval. In those cases, a petition answered within the statutory deadline does not delay approval of a pending application.

- Over the 5-year period during which FDA has been reviewing 505(q) petitions, five petitions resulted in a delay in approving a total of five ANDAs.
- FDA continues to receive 505(q) petitions from ANDA and 505(b)(2) applicants and not solely from innovator companies. FDA has not yet received any 505(q) petitions from applicants for biosimilar biological product applications.
- In the FY 2011 report, FDA stated that it had received serial 505(q) petitions, frequently from the same petitioner, about the same specific drug or class of drugs, sometimes requiring several separate responses about different issues regarding the same product. FDA stated that in addition, petitioners were raising their arguments serially, rather than asserting all available arguments in the first petition submitted. In the FY 2011 report, FDA noted that, for example, the agency received its fourth 505(q) petition relating to the approval of ANDAs for topical ophthalmic products and a third 505(q) petition related to Doryx. The various submissions raised different scientific issues, requiring serial review of different arguments, rather than one comprehensive review of all pertinent arguments. The agency responded to all of these petitions within the statutory deadline. Responding to such serial petitions requires the use of substantial FDA resources, on a repeated basis, over a protracted period of time. FDA is continuing to monitor whether this trend will continue.
- The enactment of FDASIA has increased the agency resource requirements for responding to 505(q) petitions. Section 1135 of FDASIA significantly shortened the time frame by 30 days and has given FDA less time to evaluate the issues, articulate its scientific and legal reasoning, and formulate a response on the issues referenced in the petition. As a result, FDA has needed to direct resources away from other important initiatives to attempt to comply with the new shorter deadline.

FDA will continue to gain additional experience and monitor trend data in the FY 2013 reporting period to assist Congress in determining whether section 505(q) of the FD&C Act is accomplishing the stated goals of the legislation. Based on the petitions that FDA has seen to date, however, the agency is concerned that section 505(q) may not be discouraging the submission of petitions that do not raise valid scientific issues and are intended primarily to delay the approval of competing drug products. Though many 505(q) petitions do not necessarily raise issues that are important to the public health, the statute requires FDA to prioritize these petitions above other matters, such as safety petitions, that do raise important public health concerns. FDA also believes that innovator companies may be implementing strategies to file serial 505(q) petitions and petitions for reconsideration in an effort to delay approval of ANDAs or 505(b)(2) applications for competing drugs. In addition, with the shortened timeframe under FDASIA, FDA remains concerned about the resources required to respond to 505(q) petitions within the statutory deadline at the expense of completing the other work of the agency.

## **REPORT TO CONGRESS**

**Sixth Annual Report on Delays in Approvals of  
Applications Related to Citizen Petitions and  
Petitions for Stay of Agency Action  
for Fiscal Year 2013**

**Required by Section 914 of the Food and Drug Administration  
Amendments Act of 2007**

**Public Law 110-85**

**Department of Health and Human Services  
Food and Drug Administration**

## I. STATUTORY REQUIREMENT

The Food and Drug Administration Amendments Act of 2007 (FDAAA) was enacted on September 27, 2007. Section 914 of Title IX of FDAAA took effect on the date of enactment and amended section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) by adding new subsection (q). Section 505(q) applies to certain petitions that request that the Food and Drug Administration (FDA or the Agency) take any form of action related to a pending drug approval application submitted under section 505(b)(2) or 505(j) of the FD&C Act or section 351(k) of the Public Health Service Act (PHS Act).<sup>1</sup> Section 505(q) also governs the manner in which these petitions are treated. Under section 505(q)(3) of the FD&C Act, FDA is required to submit an annual report to Congress.

The Food and Drug Administration Safety and Innovation Act (FDASIA) was signed into law on July 9, 2012 (Pub. L. 112-144, 126 Stat. 993). Section 1135 of FDASIA amended section 505(q) of the FD&C Act in two ways. First, it shortened FDA's deadline from 180 days to 150 days for responding to petitions subject to section 505(q). Second, it expanded the scope of section 505(q) to include certain petitions concerning applications submitted under section 351(k) of the PHS Act, the abbreviated pathway for the approval of biosimilar biological products. Accordingly, FDA is now including biosimilar biological product applications in the annual reports.

## II. BACKGROUND

### A. Citizen Petitions and Petitions for Stay of Agency Action

A citizen petition is a vehicle that stakeholders outside of FDA can use to ask the Agency "to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action" (21 CFR 10.25(a) and 10.30). Under the governing regulations, petitioners can request, for example, that the Agency:

- Disapprove a drug product application;
- Add warnings to the labeling of a drug; and/or
- Change products from prescription to over-the-counter (OTC) status.

FDA regulations also provide for the submission of petitions for "stay of action" to delay the effective date of an administrative action, such as the approval of certain drug applications (21 CFR 10.35). In this report, we will collectively refer to both citizen petitions and petitions for stay of Agency action as "petitions" and will refer to petitions subject to section 505(q) of the FD&C Act as "505(q) petitions."

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<sup>1</sup> In this report, an application submitted in accordance with section 505(b)(2) of the FD&C Act is referred to as a *505(b)(2) application*; an application submitted under section 505(j) of the FD&C Act is referred to as an *abbreviated new drug application (ANDA)*; and an application submitted under section 351(k) of the PHS Act is referred to as a *biosimilar biological product application*.

## B. Delays of Approvals

Section 505(q)(1)(A), together with section 505(q)(5), describes the general scope of section 505(q). Section 505(q)(1)(A) provides that:

The Secretary shall not delay approval of a pending application submitted under subsection (b)(2) or (j) of [section 505 of the FD&C Act] or section 351(k) of the Public Health Service Act because of any request to take any form of action relating to the application, either before or during consideration of the request, unless—

- (i) the request is in writing and is a petition submitted to the Secretary pursuant to section 10.30 or 10.35 of title 21, Code of Federal Regulations (or any successor regulations); and
- (ii) the Secretary determines, upon reviewing the petition, that a delay is necessary to protect the public health.

Consideration of the petition shall be separate and apart from review and approval of any application.<sup>2</sup>

In section 505(q)(5), the term *application* is defined as an application submitted under section 505(b)(2) or 505(j) of the FD&C Act or section 351(k) of the PHS Act, and the term *petition* is defined as a request described in section 505(q)(1)(A)(i) (i.e., a written request submitted in accordance with 21 CFR 10.30 or 10.35).

If FDA determines, based on a petition requesting action on a pending abbreviated new drug application (ANDA), 505(b)(2) application, or biosimilar biological product application, that a delay of approval of a pending application is necessary to protect the public health, FDA is required to provide to the applicant, no later than 30 days after making the determination, the following information:

- Notification that the determination has been made;
- If applicable, any clarification or additional data that the applicant should submit to the petition docket to allow FDA to review the petition promptly; and
- A brief summary of the specific substantive issues raised in the petition which form the basis of the determination.<sup>3</sup>

At FDA's discretion, the information described above is to be conveyed to the applicant either in a written document or through a meeting with the applicant.<sup>4</sup> The information conveyed as part of the notification is to be considered part of the application and subject to applicable disclosure requirements.<sup>5</sup>

<sup>2</sup> This sentence was added as a technical correction to FDAAA in Public Law 110-316, 122 Stat. 3509, 3524, section 301, enacted August 14, 2008.

<sup>3</sup> FD&C Act, section 505(q)(1)(B).

<sup>4</sup> FD&C Act, section 505(q)(1)(C).

<sup>5</sup> FD&C Act, section 505(q)(1)(D).

### **III. INFORMATION REPORTED**

Section 505(q)(3) of the FD&C Act requires FDA to submit an annual report to Congress containing statistical information regarding the approval of certain applications and the effect, if any, that 505(q) petitions have had on the timing of such approvals. This annual report complies with the statutory reporting requirements for FY 2013, based on data from October 1, 2012, through September 30, 2013.

The statute requires the following information to be included in the report:

- The number of ANDAs, 505(b)(2) applications, and biosimilar biological product applications approved during the reporting period;
- The number of such applications that were delayed by 505(q) petitions;
- The number of days by which the applications were delayed; and
- The number of 505(q) petitions that were submitted during the reporting period.

Between September 27, 2007, and September 30, 2013, FDA determined that a delay in approving an ANDA was necessary to protect the public health in the case of seven ANDAs with related 505(q) petitions. FDA has not delayed approval of any 505(b)(2) applications or biosimilar biological product applications based on 505(q) petitions.

During the FY 2013 reporting period, the Agency approved 37 applications submitted under section 505(b)(2), 440 ANDAs, and no biosimilar biological product applications. No approvals for any 505(b)(2) or biosimilar biological product applications were delayed because of the filing of a 505(q) petition in this reporting period. Two ANDA approvals were delayed in this reporting period because of pending 505(q) petitions.

FDA's decision to delay the approval of two pending ANDAs during this reporting period was based on the Agency's assessment that further review of the issues raised in the 505(q) petition was required to fully assess the petitioners' arguments against approval. FDA was concerned that if it approved the ANDAs before resolving the issues raised in the petition and later concluded that one or more of the arguments against approval were meritorious, then the presence on the market of drug products that did not meet the requirements for approval could negatively affect public health. Thus, FDA delayed approval of the two products at issue for 25 days to complete its analysis of the issues raised in the petitions. After FDA completed its review, the Agency determined that further delay of approval of the ANDAs was not necessary to protect the public health.

### **IV. IMPLEMENTATION DISCUSSION**

FDA has been implementing the provisions of section 505(q) for approximately 6 years. The Agency has done so by issuing guidance to encourage industry to use the 505(q) process appropriately, by proposing a regulation, and by reviewing and responding to the more than 100 petitions subject to section 505(q) that have been submitted during the 6-year period.

#### **A. Guidance**

In January 2009, the Agency issued a draft guidance for industry entitled *Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act*. In June 2011, FDA issued the final guidance ([www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079353.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079353.pdf)). The final guidance addresses the Agency's current thinking on the following topics:

- How FDA determines whether a particular petition would delay approval of a pending ANDA or 505(b)(2) application and, therefore, would fall within section 505(q);
- How FDA interprets the certification and verification requirements under section 505(q); and
- The relationship between the review of petitions and the review of pending ANDAs and 505(b)(2) applications for which FDA has not yet made a decision on approvability.

FDA plans to revise the final guidance to address the two FDASIA-related amendments to section 505(q) discussed in Section I.

#### **B. Proposed Regulation**

In January 2012 (77 FR 25), FDA published a proposed rule entitled *Amendments to Regulations on Citizen Petitions, Petitions for Stay of Action, and Submission of Documents to Dockets*. The proposed rule outlined proposed amendments to certain regulations relating to citizen petitions, petitions for stay of action, and submission of documents to the Agency. FDA proposed to add new section 10.31 (21 CFR 10.31), which includes the following provisions:

- Proposed section 10.31(a) states that section 10.31 would encompass all citizen petitions and petitions for stay of action that request that the Agency take any action that could, if taken, delay approval of an ANDA or 505(b)(2) application (i.e., citizen petitions and petitions for stay of action that are or may be subject to section 505(q) of the FD&C Act).
- Proposed section 10.31(b) would clarify the date of submission for petitions submitted under section 10.31.
- Proposed section 10.31(c) and (d) would codify the certification and verification requirements of section 505(q)(1)(H) and (I).

The comment period for this proposed rule has closed, and FDA currently is reviewing all of the comments submitted. FDA is also evaluating the impact of the two FDASIA-related amendments to section 505(q) on the provisions proposed in this rulemaking.

### C. Petition Review and Observations

During FY 2008 through FY 2013, FDA received a total of 131 petitions subject to section 505(q). Over this 6-year period, FDA responded to all but six of the 505(q) petitions within the statutory time frame that was applicable during that period.<sup>6</sup>

FDA continues to monitor the number and nature of 505(q) petitions submitted and to analyze whether section 505(q) is effectively discouraging petitioners from submitting petitions primarily to delay the approval of applications. FDA also is closely monitoring the effect of 505(q) petitions and the statutory response period for these petitions on the other work of the Agency. Although FDA generally met the statutory deadlines, it did so in part by redirecting efforts that otherwise would have been directed to other work, including responding to other citizen petitions.

It is difficult to determine whether section 505(q) is discouraging the filing of citizen petitions aimed at blocking generic competition. However, since the passage of FDAAA, the number of 505(q) petitions submitted annually has been steady—in 4 out of 6 fiscal years, FDA received approximately 20 such petitions. Table 1 shows the number of citizen petitions received by the Center for Drug Evaluation and Research (CDER) each year from 2008 through September 30, 2013, the number of petitions that were subject to section 505(q), and the percentage of all CDER petitions that were subject to section 505(q).

Table 1  
Percentage of 505(q) Petitions Received  
During Fiscal Years 2008-2013

FY	No. of Petitions <sup>7</sup>	No. of 505(q) petitions	% of petitions that were 505(q) petitions
'08	78	21	27
'09	81	31	38
'10	76	20	26
'11	96	20	21
'12	94	24	26
'13	92	15	16

<sup>6</sup> The 180-day statutory time frame for responding to 505(q) petitions was reduced to 150 days by section 1135 of FDASIA.

<sup>7</sup> This represents the number of petitions handled by CDER, excluding suitability petitions and petitions that raise only OTC monograph issues.

Table 2 below summarizes the outcomes for the 124 petitions that have been resolved under section 505(q) as of September 30, 2013.

Table 2  
Outcomes Of 505(q) Petitions  
Resolved During Fiscal Years 2008-2013<sup>8</sup>

	FY	Denied	Granted	Denied/ Granted in Part	Withdrawn	Total # of Determinations
Fiscal Year	'08	10	1	3	0	14
	'09	16	2	6	0	24
	'10	16	2	6	0	24
	'11	10	1	9	2	22
	'12	10	1	2	0	13
	'13	21	1	5	0	27
	Total	83	8	31	2	124

Outcomes:

- **Denied**: FDA denied the petition's requests. This includes instances where FDA issued a denial without comment on the substance of one or more of the requests.
- **Granted**: FDA granted the petition's requests.
- **Denied in Part, Granted in Part**: FDA denied some of the petition's requests and granted others. This includes instances where FDA denied one or more of the requests without comment on the substance of the request.
- **Withdrawn**: The petitioner withdrew the petition.

As of September 30, 2013, 83 of the petitions (approximately 67 percent) responded to under section 505(q) have been denied. Another 31 petitions (approximately 25 percent) have been denied in part and granted in part. Only eight petitions (approximately 6.5 percent) have been granted. An additional two petitions, approximately 1.5 percent, were voluntarily withdrawn by the petitioner.

Some of the trends in 505(q) petitions that FDA believes may be relevant are as follows:

- In many instances, the statutory deadline for responding to a 505(q) petition occurs before any related ANDAs or 505(b)(2) applications are ready for approval. In those cases, a petition answered within the statutory deadline does not delay approval of a pending application.

<sup>8</sup> The number of petitions resolved in each year does not match the number submitted in that year (see Table 1) because in many cases petitions received in a given year are not resolved until the following year.

- Over the 6-year period during which FDA has been reviewing 505(q) petitions, six petitions resulted in a delay in approving a total of seven ANDAs. The six petitions represent less than 5 percent of all 505(q) petitions received over this 6-year period; the seven ANDAs delayed are a very small percentage (<1 percent) of all ANDAs received over the same time period.
- FDA had not received any 505(q) petitions regarding biosimilar biological product applications through September 30, 2013.
- FDA continues to receive serial 505(q) petitions, frequently from the same petitioner, about the same specific drug or class of drugs, sometimes requiring several separate responses about different issues regarding the same product. Responding to such serial petitions requires the use of substantial FDA resources, on a repeated basis, over a protracted period of time.
- The enactment of FDASIA has increased the strain on Agency resources for responding to 505(q) petitions. Section 1135 of FDASIA significantly shortened the time frame by 30 days and has given FDA less time to evaluate the issues, articulate its scientific and legal reasoning, and formulate a response on the issues referenced in the petition. As a result, FDA has needed to direct resources away from other important initiatives to attempt to comply with the new shorter deadline.
- 505(q) contains a provision that permits FDA to summarily deny a petition at any point if FDA finds that it was submitted with the primary purpose of delaying the approval of an ANDA or 505(b)(2) application and the petition does not “on its face” raise valid scientific or regulatory issues (FD&C Act, section 505(q)(1)(E)). As FDA previously noted in its report to Congress entitled “Encouraging Early Submission of Citizen Petitions and Petitions for Stay of Agency Action,” dated February 2009, we believe that the statutory language requires that both preconditions be present, and we believe this statutory standard would be extremely difficult to meet. To date, FDA has never applied this provision to summarily deny a petition, despite the fact that, in FDA’s estimation, many 505(q) petitions do not in fact raise persuasive scientific or regulatory issues when those issues have been reviewed by FDA (as previously noted, approximately two-thirds of these petitions are denied in full). Accordingly, it is FDA’s view that this provision has neither curbed the filing of frivolous petitions submitted with the primary purpose of delay, nor has it permitted FDA to dispose of such petitions without expending substantial amounts of resources.

The Agency is concerned that section 505(q) is not discouraging the submission of petitions that are intended primarily to delay the approval of competing drug products and that do not raise valid scientific issues. The statute requires FDA to prioritize these petitions above other matters, such as safety petitions, that do raise important public health concerns. FDA also believes that innovator companies are, in some cases, implementing strategies to file serial 505(q) petitions and petitions for reconsideration in an effort to delay approval of ANDAs or 505(b)(2) applications for competing drugs. In addition, with the shortened timeframe under FDASIA, FDA remains concerned about the resources required to respond to 505(q) petitions within the statutory deadline at the expense of completing the other work of the Agency.

## REPORT TO CONGRESS

Seventh Annual Report on Delays in Approvals of  
Applications Related to Citizen Petitions and  
Petitions for Stay of Agency Action  
for Fiscal Year 2014

Required by Section 914 of the Food and Drug Administration  
Amendments Act of 2007

Public Law 110-85

Department of Health and Human Services  
Food and Drug Administration



Date AUGUST 3, 2015

Stephen M. Ostroff, M.D.  
Acting Commissioner of Food and Drugs

## EXECUTIVE SUMMARY

Section 505(q) of the Food, Drug, and Cosmetic Act (FD&C Act) applies to certain petitions that request that the Food and Drug Administration (FDA or Agency) take any form of action related to a pending drug approval application submitted under section 505(b)(2) or 505(j) of the FD&C Act or section 351(k) of the Public Health Service Act (PHS Act). Under section 505(q)(3) of the FD&C Act, FDA is required to submit an annual report to Congress that includes the following information:

- The number of abbreviated new drug applications (ANDAs), 505(b)(2) applications, and biosimilar biological product applications approved during the reporting period;
- The number of such applications that were delayed by 505(q) petitions;
- The number of days by which the applications were delayed; and
- The number of 505(q) petitions that were submitted during the reporting period.

During the fiscal year (FY) 2014 reporting period, FDA approved 39 505(b)(2) applications, 409 ANDAs, and 0 biosimilar biological product applications. No approvals for ANDAs or biosimilar biological product applications were delayed because of a 505(q) petition in this reporting period. One 505(b)(2) application approval was delayed in this reporting period because of a 505(q) petition. During FY 2014, FDA received 28 505(q) petitions.

FDA has reviewed the data regarding the numbers of 505(q) petitions received during FY 2008-2014 (Table 1), the outcomes of 505(q) petitions resolved during FY 2008-2014 (Table 2), and the number of petitions resulting in approval delays during FY 2008-2014 (Table 3). Based on its analysis, FDA continues to be concerned that section 505(q) is not discouraging the submission of petitions that are intended primarily to delay the approval of competing drug products and do not raise valid scientific issues. However, the statute requires FDA to prioritize these petitions above other matters, such as safety petitions, that do raise important public health concerns. Although FDA has generally met the statutory deadlines for 505(q) petitions, it did so in part by redirecting efforts that otherwise would have been directed to other work, including responding to other citizen petitions. FDA remains concerned about the resources required to respond to 505(q) petitions within the statutory deadline at the expense of completing the other work of the Agency.

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## I. STATUTORY REQUIREMENT

The Food and Drug Administration Amendments Act of 2007 (FDAAA) was enacted on September 27, 2007. Section 914 of Title IX of FDAAA took effect on the date of enactment and amended section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) by adding new subsection (q). Section 505(q) applies to certain petitions that request that the Food and Drug Administration (FDA or Agency) take any form of action related to a pending drug approval application submitted under section 505(b)(2) or 505(j) of the FD&C Act or section 351(k) of the Public Health Service Act (PHS Act).<sup>1</sup> Section 505(q) also governs the manner in which these petitions are treated. Under section 505(q)(3) of the FD&C Act, FDA is required to submit an annual report to Congress.

The Food and Drug Administration Safety and Innovation Act (FDASIA) was signed into law on July 9, 2012 (Pub. L. 112-144, 126 Stat. 993). Section 1135 of FDASIA amended section 505(q) of the FD&C Act in two ways. First, it shortened FDA's deadline from 180 days to 150 days for responding to petitions subject to section 505(q). Second, it expanded the scope of section 505(q) to include certain petitions concerning applications submitted under section 351(k) of the PHS Act, the abbreviated pathway for the approval of biosimilar biological products. Accordingly, we are now including biosimilar biological product applications in our annual reports.

## II. BACKGROUND

### A. Citizen Petitions and Petitions for Stay of Agency Action

A citizen petition is a vehicle that stakeholders outside of FDA can use to ask FDA "to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action" (21 CFR 10.25(a) and 10.30). Under the governing regulations, petitioners can request, for example, that the Agency:

- Disapprove a drug product application;
- Add warnings to the labeling of a drug; and/or
- Change products from prescription to over-the-counter (OTC) status.

FDA regulations also provide for the submission of petitions for "stay of action" to delay the effective date of an administrative action, such as the approval of certain drug applications (21 CFR 10.35). In this report, we will collectively refer to both citizen petitions and petitions for stay of Agency action as "petitions" and will refer to petitions subject to section 505(q) of the FD&C Act as "505(q) petitions."

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<sup>1</sup> In this report, an application submitted in accordance with section 505(b)(2) of the FD&C Act is referred to as a *505(b)(2) application*; an application submitted under section 505(j) of the FD&C Act is referred to as an *abbreviated new drug application (ANDA)*; and an application submitted under section 351(k) of the PHS Act is referred to as a *biosimilar biological product application*.

## B. Delays of Approvals

Section 505(q)(1)(A), together with section 505(q)(5), describes the general scope of section 505(q). Section 505(q)(1)(A) provides:

The Secretary shall not delay approval of a pending application submitted under subsection (b)(2) or (j) of [section 505 of the FD&C Act] or section 351(k) of the Public Health Service Act because of any request to take any form of action relating to the application, either before or during consideration of the request, unless—

- (i) the request is in writing and is a petition submitted to the Secretary pursuant to section 10.30 or 10.35 of title 21, Code of Federal Regulations (or any successor regulations); and
- (ii) the Secretary determines, upon reviewing the petition, that a delay is necessary to protect the public health.

Consideration of the petition shall be separate and apart from review and approval of any application.<sup>2</sup>

In section 505(q)(5), the term *application* is defined as an application submitted under section 505(b)(2) or 505(j) of the FD&C Act or section 351(k) of the PHS Act, and the term *petition* is defined as a request described in section 505(q)(1)(A)(i) (i.e., a written request submitted in accordance with 21 CFR 10.30 or 10.35).

If FDA determines, based on a petition requesting action on a pending abbreviated new drug application (ANDA), 505(b)(2) application, or biosimilar biological product application, that a delay of approval of a pending application is necessary to protect the public health, FDA is required to provide to the applicant, not later than 30 days after making the determination, the following information:

- Notification that the determination has been made;
- If applicable, any clarification or additional data that the applicant should submit to the petition docket to allow FDA to review the petition promptly; and
- A brief summary of the specific substantive issues raised in the petition which form the basis of the determination.<sup>3</sup>

At FDA's discretion, the information described above is to be conveyed to the applicant either in a written document or through a meeting with the applicant.<sup>4</sup> The information conveyed as part of the notification is to be considered part of the application and subject to applicable disclosure requirements.<sup>5</sup>

<sup>2</sup> This sentence was added as a technical correction to FDAAA in Public Law 110-316, 122 Stat. 3509, 3524, section 301, enacted August 14, 2008.

<sup>3</sup> FD&C Act, section 505(q)(1)(B).

<sup>4</sup> FD&C Act, section 505(q)(1)(C).

<sup>5</sup> FD&C Act, section 505(q)(1)(D).

### III. INFORMATION REPORTED

Section 505(q)(3) of the FD&C Act requires FDA to submit an annual report to Congress containing statistical information regarding the approval of certain applications and the effect, if any, that 505(q) petitions have had on the timing of such approvals. This annual report complies with the statutory reporting requirements for FY 2014, based on data from October 1, 2013, through September 30, 2014.

The statute requires the following information to be included in the report:

- The number of ANDAs, 505(b)(2) applications, and biosimilar biological product applications approved during the reporting period;
- The number of such applications that were delayed by 505(q) petitions;
- The number of days by which the applications were delayed; and
- The number of 505(q) petitions that were submitted during the reporting period.

During the FY 2014 reporting period, the Agency approved 39 505(b)(2) applications, 409 ANDAs, and 0 biosimilar biological product applications. No approvals for ANDAs or biosimilar biological product applications were delayed because of a 505(q) petition in this reporting period. One 505(b)(2) application approval was delayed in this reporting period because of a 505(q) petition.

FDA's decision to delay the approval of one 505(b)(2) application during this reporting period was based on the Agency's assessment that further review of the issues raised in the 505(q) petition was required to fully assess the petitioners' arguments against approval. FDA was concerned that if it approved the 505(b)(2) application before resolving the issues raised in the petition and later concluded that one or more of the arguments against approval were meritorious, then the presence on the market of a drug product that did not meet the requirements for approval could negatively affect public health. Thus, FDA delayed approval of the product at issue for 5 days to complete its analysis of the issues raised in the petition.

### IV. IMPLEMENTATION DISCUSSION

FDA has been implementing the provisions of section 505(q) for approximately 7 years. FDA has done so by issuing guidance to encourage industry to use the 505(q) process appropriately, by proposing a regulation, and by reviewing and resolving petitions subject to section 505(q).

#### A. Guidance

In January 2009, the Agency issued draft guidance for industry titled: *Citizen Petitions and Petitions for Stay of Action Subject to section 505(q) of the Federal Food, Drug, and Cosmetic Act*.

In June 2011, FDA issued a final guidance. The final guidance addressed the Agency's current thinking on the following topics:

- How FDA determines whether a particular petition would delay approval of a pending ANDA or 505(b)(2) application and, therefore, would fall within section 505(q);
- How FDA interprets the certification and verification requirements under section 505(q); and
- The relationship between the review of petitions and the review of pending ANDAs and 505(b)(2) applications for which FDA has not yet made a decision on approvability.

After the end of FY 2014, on November 18, 2014, FDA revised the final guidance to incorporate the two FDASIA amendments to section 505(q) discussed in Section I, which shortened from 180 days to 150 days FDA's deadline for responding to petitions subject to section 505(q), and with the exceptions noted below, expanded the scope of section 505(q) to include certain petitions related to biosimilar applications. The revised final guidance is available at [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079353.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079353.pdf).

## **B. Proposed Regulation**

In January 2012 (77 FR 25), FDA published a proposed rule titled *Amendments to Regulations on Citizen Petitions, Petitions for Stay of Action, and Submission of Documents to Dockets*. The proposed rule outlined proposed amendments to certain regulations relating to citizen petitions, petitions for stay of action, and submission of documents to the Agency. FDA proposed to add new § 10.31 (21 CFR 10.31), which includes the following provisions:

- Proposed § 10.31(a) states that § 10.31 would encompass all citizen petitions and petitions for stay of action that request that the Agency take any action that could, if taken, delay approval of an ANDA or 505(b)(2) application (i.e., citizen petitions and petitions for stay of action that are or may be subject to section 505(q) of the FD&C Act).
- Proposed § 10.31(b) would clarify the date of submission for petitions submitted under § 10.31.
- Proposed § 10.31(c) and (d) would codify the certification and verification requirements of section 505(q)(1)(H) and (I).

The comment period for this proposed rule has closed, and FDA currently is reviewing all of the comments submitted. FDA also is evaluating the impact of the two FDASIA-related amendments to section 505(q) on the provisions proposed in this rulemaking.

### C. Petition Review and Observations

During FY 2008 through FY 2014, FDA received a total of 160 petitions subject to section 505(q). Over this 7-year period, FDA responded to all but nine of the 505(q) petitions within the statutory time frame that was applicable during that period.<sup>6</sup>

FDA continues to monitor the number and nature of 505(q) petitions submitted and continues to analyze whether section 505(q) is effectively discouraging petitioners from submitting petitions primarily to delay the approval of applications. FDA also is closely monitoring the effect of 505(q) petitions and the statutory response period for these petitions on the other work of the Agency. Although FDA has generally met the statutory deadlines, it did so in part by redirecting efforts that otherwise would have been directed to other work, including responding to other citizen petitions.

It is difficult to determine whether section 505(q) is discouraging the filing of citizen petitions aimed at blocking generic competition. Table 1 shows the number of citizen petitions received by CDER each year from 2008 through September 30, 2014, the number of those petitions that were subject to section 505(q), and the percentage of all CDER petitions that were subject to section 505(q).

Table 1  
Percentage of 505(q) Petitions Received  
During Fiscal Years 2008-2014

FY	No. of Petitions <sup>7</sup>	No. of 505(q) petitions	% of petitions that were 505(q) petitions
'08	78	21	27
'09	81	31	38
'10	76	20	26
'11	96	20	21
'12	94	24	26
'13	92	15	16
'14	102	28	27

<sup>6</sup> The 180-day timeframe applied to petitions submitted on or after September 27, 2007, the date on which Section 505(q) was initially effective, through July 8, 2012. Effective July 9, 2012, the amendments in FDASIA reduced the timeframe to 150 days.

<sup>7</sup> This represents the number of petitions handled by the Center for Drug Evaluation and Research, excluding suitability petitions and petitions that raise only OTC monograph issues.

Table 2 below summarizes the outcomes for the 149 petitions that have been resolved under section 505(q) as of September 30, 2014.

Table 2  
Outcomes Of 505(q) Petitions  
Resolved During Fiscal Years 2008-2014<sup>8</sup>

	FY	Denied	Granted	Denied/ Granted in Part	Withdrawn	Total # of Determinations
Fiscal Year	'08	10	1	3	0	14
	'09	16	2	6	0	24
	'10	16	2	6	0	24
	'11	10	1	9	2	22
	'12	10	1	2	0	13
	'13	21	1	5	0	27
	'14	15	0	8	2	25
	Total	98	8	39	4	149

Outcomes:

- **Denied:** FDA denied the petition's requests. This includes instances where FDA issued a denial without comment on the substance of one or more the requests.
- **Granted:** FDA granted the petition's requests.
- **Denied in Part, Granted in Part:** FDA denied some of the petition's requests and granted others. This includes instances where FDA denied one or more of the requests without comment on the substance of the request.
- **Withdrawn:** The petitioner withdrew the petition.

As of September 30, 2014, 98 of the petitions (approximately 66 percent) responded to under section 505(q) have been denied. Another 39 petitions (approximately 26 percent) have been denied in part and granted in part. Only 8 petitions (approximately 5 percent) have been granted. An additional 4 petitions, approximately 3 percent were voluntarily withdrawn by the petitioner.

<sup>8</sup> The number of petitions resolved in each year does not match the number submitted in that year (see Table 1) because in many cases petitions received in a given year are not resolved until the following year.

Table 3  
Petitions Resulting in Approval Delays  
During Fiscal Years 2008-2014

	FY	# of Petitions	# of Delayed Approvals
Fiscal Year	'08	1	2 ANDAs
	'09	1	1 ANDA
	'10	1	1 ANDA
	'11	1	1 ANDA
	'12	0	0
	'13	1	2 ANDAs
	'14	1	1 505(b)(2)
	Total	6	8

Some of the trends in 505(q) petitions that FDA believes may be relevant are as follows:

- In many instances, the statutory deadline for responding to a 505(q) petition occurs before any related ANDAs or 505(b)(2) applications are ready for approval. In those cases, a petition answered within the statutory deadline does not delay approval of a pending application.
- Over the 7-year period during which FDA has been reviewing 505(q) petitions, six petitions resulted in a delay in approving a total of seven ANDAs. The six petitions represent 4 percent of all 505(q) petitions received over this 7-year period; the seven ANDAs delayed are a very small percentage (<1 percent) of all ANDAs received over the same time period.
- Over the 7-year period during which FDA has been reviewing 505(q) petitions, one petition resulted in a delay in approving one 505(b)(2) application. This petition represents 0.7 percent (<1 percent) of all 505(q) petitions received over this 7-year period; the 505(b)(2) application delayed represents a very small percentage 0.004 (<1 percent) of all 505(b)(2) applications approved over the same time period.
- FDA had not received any 505(q) petitions regarding biosimilar biological product applications through September 30, 2014.

- FDA continues to receive serial 505(q) petitions, frequently from the same petitioner, about the same specific drug or class of drugs, sometimes requiring several separate responses about different issues regarding the same product. Responding to such serial petitions requires the use of substantial FDA resources, on a repeated basis, over a protracted period of time.
- The enactment of FDASIA has increased the strain on Agency resources by significantly shortening the time frame for responding to 505(q) petitions by 30 days. The shortened timeframe affords FDA even less time to evaluate the issues raised in the petitions and to provide a response that articulates the scientific and legal reasoning supporting the Agency's decision. As a result, FDA has needed to direct resources away from other important initiatives to attempt to comply with the new shorter deadline.
- 505(q) contains a provision that permits FDA to summarily deny a petition at any point if FDA finds that it was submitted with the primary purpose of delaying the approval of an ANDA, 505(b)(2) application, or 351(k) application and the petition does not "on its face" raise valid scientific or regulatory issues (FD&C Act, section 505(q)(1)(E)). As FDA previously noted in its Report to Congress, "Encouraging Early Submission of Citizen Petitions and Petitions for Stay of Agency Action" dated February 2009, we believe that the statutory language requires that both preconditions be present, and we believe this statutory standard would be extremely difficult to meet. To date, FDA has never applied this provision to summarily deny a petition, despite the fact that, in FDA's estimation, many 505(q) petitions do not in fact raise persuasive scientific or regulatory issues when those issues have been reviewed by FDA (as previously noted, approximately two-thirds of these petitions are denied in full). Accordingly, it is FDA's view that this provision has neither curbed the filing of petitions submitted with the primary purpose of delay nor has it permitted FDA to dispose of such petitions without expending substantial amounts of resources.

#### **D. Conclusions**

The Agency continues to be concerned that section 505(q) is not discouraging the submission of petitions that are intended primarily to delay the approval of competing drug products and do not raise valid scientific issues. The statute requires FDA to prioritize these petitions above other matters, such as safety petitions, that do raise important public health concerns. As a result, FDA remains concerned about the resources required to respond to 505(q) petitions within the 150 day deadline at the expense of completing the other work of the Agency.


## REPORT TO CONGRESS

Eighth Annual Report on Delays in Approvals of  
Applications Related to Citizen Petitions and  
Petitions for Stay of Agency Action  
for Fiscal Year 2015

Required by Section 914 of the Food and Drug Administration  
Amendments Act of 2007

Public Law 110-85

Department of Health and Human Services  
Food and Drug Administration

  
\_\_\_\_\_  
Robert M. Califf, M.D.  
Commissioner of Food and Drugs

Date 7-29-16

## EXECUTIVE SUMMARY

Section 505(q) of the Food, Drug, and Cosmetic Act (FD&C Act) applies to certain petitions that request that the Food and Drug Administration (FDA or Agency) take any form of action related to a pending drug approval application submitted under section 505(b)(2) or 505(j) of the FD&C Act or section 351(k) of the Public Health Service Act (PHS Act). Under section 505(q)(3) of the FD&C Act, FDA is required to submit an annual report to Congress that includes the following information:

- The number of abbreviated new drug applications (ANDAs), 505(b)(2) applications, and biosimilar biological product applications approved during the reporting period;
- The number of such applications that were delayed by 505(q) petitions;
- The number of days by which the applications were delayed; and
- The number of 505(q) petitions that were submitted during the reporting period.

During the fiscal year (FY) 2015 reporting period, FDA approved 492 ANDAs, 45 505(b)(2) applications, and 1 biosimilar biological product application. No approvals for biosimilar biological product applications were delayed because of a 505(q) petition in this reporting period. The approval of one ANDA was delayed because of two 505(q) petitions, and the approval of one 505(b)(2) application was delayed because of one 505(q) petition. During FY 2015, FDA received 15 505(q) petitions.

FDA has reviewed the data regarding the numbers of 505(q) petitions received during FY 2008-2015 (Table 1), the outcomes of 505(q) petitions resolved during FY 2008-2015 (Table 2), and the number of petitions resulting in approval delays during FY 2008-2015 (Table 3). Based on its analysis, FDA continues to be concerned that section 505(q) may not be discouraging the submission of petitions that are intended primarily to delay the approval of competing drug products and do not raise valid scientific issues. However, the statute requires FDA to prioritize these petitions above other matters, such as safety petitions, that do raise important public health concerns. Although FDA has generally met the statutory deadlines for 505(q) petitions, it did so in part by redirecting efforts that otherwise would have been directed to other work, including responding to other citizen petitions. FDA remains concerned about the resources required to respond to 505(q) petitions within the statutory deadline at the expense of completing the other work of the Agency.

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## I. STATUTORY REQUIREMENT

The Food and Drug Administration Amendments Act of 2007 (FDAAA) was enacted on September 27, 2007. Section 914 of Title IX of FDAAA took effect on the date of enactment and amended section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) by adding new subsection (q). The Food and Drug Administration Safety and Innovation Act (FDASIA) was signed into law on July 9, 2012 (Pub. L. 112-144, 126 Stat. 993). Section 1135 of FDASIA amended section 505(q) of the FD&C Act.

Section 505(q) applies to certain petitions that request that the Food and Drug Administration (FDA or Agency) take any form of action related to a pending drug approval application submitted under the abbreviated approval pathways described in section 505(b)(2) or section 505(j) of the FD&C Act or in the biosimilars approval pathway described in section 351(k) of the Public Health Service Act (PHS Act).<sup>1</sup> Section 505(q) also governs the manner in which these petitions are treated. Under section 505(q)(3) of the FD&C Act, FDA is required to submit an annual report to Congress.

## II. BACKGROUND

### A. Citizen Petitions and Petitions for Stay of Agency Action

A citizen petition is a vehicle that stakeholders outside of FDA can use to ask FDA “to issue, amend, or revoke a regulation or order, or to take or refrain from taking any other form of administrative action” (21 CFR 10.25(a) and 10.30). Under the governing regulations, petitioners can request, for example, that the Agency:

- Disapprove a drug product application;
- Add warnings to the labeling of a drug; and/or
- Change products from prescription to over-the-counter (OTC) status.

FDA regulations also provide for the submission of petitions for “stay of action” to delay the effective date of an administrative action, such as the approval of certain drug applications (21 CFR 10.35). In this report, we will collectively refer to both citizen petitions and petitions for stay of Agency action as “petitions” and will refer to petitions subject to section 505(q) of the FD&C Act as “505(q) petitions.”

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<sup>1</sup> In this report, an application submitted in accordance with section 505(b)(2) of the FD&C Act is referred to as a *505(b)(2) application*; an application submitted under section 505(j) of the FD&C Act is referred to as an *abbreviated new drug application (ANDA)*; and an application submitted under section 351(k) of the PHS Act is referred to as a *biosimilar biological product application*. The Center for Drug Evaluation and Research (CDER) is responsible for responding to petitions submitted under section 505(q).

**B. Delays of Approvals**

Section 505(q)(1)(A), together with section 505(q)(5), describes the general scope of section 505(q). Section 505(q)(1)(A) provides:

The Secretary shall not delay approval of a pending application submitted under subsection (b)(2) or (j) of [section 505 of the FD&C Act] or section 351(k) of the Public Health Service Act because of any request to take any form of action relating to the application, either before or during consideration of the request, unless—

- (i) the request is in writing and is a petition submitted to the Secretary pursuant to section 10.30 or 10.35 of title 21, Code of Federal Regulations (or any successor regulations); and
- (ii) the Secretary determines, upon reviewing the petition, that a delay is necessary to protect the public health.

Consideration of the petition shall be separate and apart from review and approval of any application.<sup>2</sup>

In section 505(q)(5), the term *application* is defined as an application submitted under section 505(b)(2) or 505(j) of the FD&C Act or section 351(k) of the PHS Act, and the term *petition* is defined as a request described in section 505(q)(1)(A)(i) (i.e., a written request submitted in accordance with 21 CFR 10.30 or 10.35).

If FDA determines—based on a petition requesting action on a pending abbreviated new drug application (ANDA), 505(b)(2) application, or biosimilar biological product application—that a delay of approval of a pending application is necessary to protect the public health, FDA is required to provide to the applicant, not later than 30 days after making the determination, the following information:

- Notification that the determination has been made;
- If applicable, any clarification or additional data that the applicant should submit to the petition docket to allow FDA to review the petition promptly; and
- A brief summary of the specific substantive issues raised in the petition which form the basis of the determination.<sup>3</sup>

At FDA's discretion, the information described above is to be conveyed to the applicant either in a written document or through a meeting with the applicant.<sup>4</sup> The information conveyed as part of the notification is to be considered part of the application and subject to applicable disclosure requirements.<sup>5</sup>

<sup>2</sup> This sentence was added as a technical correction to FDAAA in Public Law 110-316, 122 Stat. 3509, 3524, section 301, enacted August 14, 2008.

<sup>3</sup> FD&C Act, section 505(q)(1)(B).

<sup>4</sup> FD&C Act, section 505(q)(1)(C).

<sup>5</sup> FD&C Act, section 505(q)(1)(D).

### III. INFORMATION REPORTED

Section 505(q)(3) of the FD&C Act requires FDA to submit an annual report to Congress containing statistical information regarding the approval of certain applications and the effect, if any, that 505(q) petitions have had on the timing of such approvals. This annual report complies with the statutory reporting requirements for FY 2015, based on data from October 1, 2014, through September 30, 2015.

The statute requires the following information to be included in the report:

- The number of ANDAs, 505(b)(2) applications, and biosimilar biological product applications approved during the reporting period;
- The number of such applications that were delayed by 505(q) petitions;
- The number of days by which the applications were delayed; and
- The number of 505(q) petitions that were submitted during the reporting period.

During the FY 2015 reporting period, the Agency approved 492 ANDAs, 45 505(b)(2) applications, and 1 biosimilar biological product application. The approval of one 505(b)(2) application was delayed because of one 505(q) petition, and the approval of one ANDA was delayed because of two 505(q) petitions. No approvals for biosimilar biological product applications were delayed because of a 505(q) petition in this reporting period.

FDA's decision to delay the approval of one ANDA application and one 505(b)(2) application during this reporting period was based on the Agency's assessment that further review of the issues raised in the 505(q) petitions was required to fully assess the petitioners' arguments against approval. FDA was concerned that if it approved the ANDA and 505(b)(2) applications before resolving the issues raised in the petitions and later concluded that one or more of the arguments against approval were meritorious, then the presence on the market of a drug product that did not meet the requirements for approval could negatively affect public health. Thus, FDA delayed approval of the ANDA and 505(b)(2) applications for 141 and 44 days, respectively, to complete an analysis of the issues raised in the petitions.

### IV. PETITION REVIEW AND OBSERVATIONS

From FY 2008 through FY 2015, FDA received a total of 175 petitions subject to section 505(q). Over this 8-year period, FDA responded to all but 11 of the 505(q) petitions within the statutory time frame that was applicable during that period.<sup>6</sup>

FDA continues to monitor the number and nature of 505(q) petitions submitted and continues to analyze whether section 505(q) is effectively discouraging petitioners from submitting petitions primarily to delay the approval of applications. FDA also is closely monitoring the effect of 505(q) petitions and the statutory response period for these petitions on the other work of the

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<sup>6</sup> The 180-day timeframe applied to petitions submitted on or after September 27, 2007 (the date on which section 505(q) was initially effective), through July 8, 2012. Effective July 9, 2012, the amendments in FDASIA reduced the timeframe to 150 days.

Agency. Although FDA has generally met the statutory deadlines, it did so in part by redirecting efforts that otherwise would have been directed to other work, including responding to other citizen petitions.

It is difficult to determine whether section 505(q) is discouraging the filing of citizen petitions aimed at blocking generic or biosimilar competition. Table 1 shows the number of citizen petitions received by FDA's Center for Drug Evaluation and Research (CDER) each year from 2008 through September 30, 2015; the number of those petitions that were subject to section 505(q); and the percentage of all CDER petitions that were subject to section 505(q). There are no clear trends in the data over time.

Table 1  
Percentage of 505(q) Petitions Received  
During Fiscal Years 2008-2015

FY Received	# of Petitions <sup>7</sup>	# of 505(q) petitions	Percentage of petitions that were 505(q) petitions
2008	78	21	27%
2009	81	31	38%
2010	76	20	26%
2011	96	20	21%
2012	84	25	30% <sup>8</sup>
2013	92	15	16%
2014	102	28	27%
2015	74	15	20%

Table 2 below summarizes the outcomes for the 167 petitions that have been resolved under section 505(q) as of September 30, 2015.

<sup>7</sup> This represents the number of petitions handled by CDER, excluding suitability petitions and petitions that raise only OTC monograph issues.

<sup>8</sup> These numbers for FY2012 have been corrected from previous annual reports to Congress.

Table 2  
Outcomes of 505(q) Petitions  
Resolved During Fiscal Years 2008-2015<sup>9</sup>

	FY Resolved	Denied	Granted	Denied/ Granted in Part	Withdrawn	Total # of Determinations
Fiscal Year	2008	10	1	3	0	14
	2009	16	2	6	0	24
	2010	16	2	6	0	24
	2011	10	1	9	2	22
	2012	10	1	2	0	13
	2013	21	1	5	0	27
	2014	15	0	8	2	25
	2015	16	0	2	0	18
	Total	114	8	41	4	<b>167</b>

Outcomes:

- **Denied**: FDA denied the petition's requests. This includes instances where FDA issued a denial without comment on the substance of one or more of the requests.
- **Granted**: FDA granted the petition's requests.
- **Denied in Part/Granted in Part**: FDA denied some of the petition's requests and granted others. This includes instances where FDA denied one or more of the requests without comment on the substance of the request.
- **Withdrawn**: The petitioner withdrew the petition.

As of September 30, 2015, 114 of the petitions (approximately 68 percent) responded to under section 505(q) have been denied. Another 41 petitions (approximately 25 percent) have been denied in part and granted in part. Only 8 petitions (approximately 5 percent) have been granted. An additional 4 petitions (approximately 2 percent) were voluntarily withdrawn by the petitioner.

<sup>9</sup> The number of petitions resolved in each year does not match the number submitted in that year (see Table 1) because in many cases petitions received in a given year are not resolved until the following year.

Table 3  
Petitions Resulting in Approval Delays  
During Fiscal Years 2008-2015

	FY	# of Petitions	# of Delayed Approvals
Fiscal Year	2008	1	2 ANDAs
	2009	1	1 ANDA
	2010	1	1 ANDA
	2011	1	1 ANDA
	2012	0	0
	2013	1	2 ANDAs
	2014	1	1 505(b)(2)
	2015	3	1 505(b)(2) and 1 ANDA <sup>10</sup>
	Total	9	10

## V. CONCLUSIONS

The Agency continues to be concerned that section 505(q) may not be discouraging the submission of petitions that are intended primarily to delay the approval of competing drug products and do not raise valid scientific issues. The statute requires FDA to prioritize these petitions above other matters, such as safety petitions, that do raise important public health concerns. As a result, FDA remains concerned about the resources required to respond to 505(q) petitions within the 150-day deadline at the expense of completing the other work of the Agency.

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<sup>10</sup> Two petitions impacted the approval date of the same ANDA and one petition impacted the approval date of one 505(b)(2) application.